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THE MEDICAL PROFESSION'S RESPONSIBILITY IN THE PREVENTION OF BLINDNESS*

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ONE of the main objects of this paper is to describe what is being done by the state and federal governments for those suffering from defective eyesight. The family physician is the backbone of the medical profession. His guidance and co-operation are essential in any program of care and prevention of disease. That he should be interested in the prevention of blindness might seem to be outside his professional interest. But is the eye not a part of the human body? And certainly his interest is in the human body.

Interest in the welfare of those handicapped by reason of reduced vision has been greatly stimulated by the advent of the Social Security Act. This law was passed in 1935. It makes provision for the indigent blind by paying to the participating state half of all payments up to forty dollars a month; that is, if the state grants a person forty dollars a month, the federal government reimburses twenty dollars. The state, by accepting the benefits of the provisions of this law, actually becomes a copartner of the federal government in effecting its operation. Since the federal government has assumed a part of the responsibility, it naturally follows that it will participate in carrying out the provisions of this law. The federal government has promulgated certain regulations to make the law more universally applicable to all the states, and to see that provision is made for equitable treatment and distribution of funds to all applicants for and recipients of financial assistance.

In order to facilitate its operation, the Social Security Board, soon after the act became operable, made certain definite recommendations relative to blindness. In the first place, it proposed a definition of economic blindness. Secondly, it required that certain medical data be determined and that they be kept by the state agency for each applicant for assistance, and further, it suggested that the medical examination be made *only* by an eye physician who holds a certificate of the American Board of Ophthalmology; this enables the state to have an authentic record of each person applying for aid to the blind. It developed a record form covering certain medical data, to be filled out by the eye physician after his examination. Massachusetts used the suggested form until recently, when the Medical Advisory Committee and the director of the Division of the Blind composed a new form that includes all the requirements set up by the Board but is developed in a way that best meets the need in Massachusetts. This form requires an accurate description of each eye, and a statement concerning the primary cause of blindness. The etiologic cause of blindness is required, a factor that eventually will establish authentic data that can be used as the basis of a real prevention program. Finally, the Board suggested the appointment of a trained ophthalmologist to review all medical reports.

Many of the states have appointed specialists to head their medical activities as supervising ophthalmologists. It is the duty of the supervising ophthalmologist to review the medical report of each applicant for blind relief. If the report is incomplete or unsatisfactory, a re-examination is required. When there is a doubt in the mind of the supervising ophthalmologist concerning the facts reported, he requests that the applicant appear before him for examination. In some states medical reports on all blind persons requesting any type of service from the state are required. In New York, medical forms on all blind persons who may become known to any public-welfare department are filed with the Commission for the Blind. These are catalogued so that with the aid of this file studies of any one cause of blindness can be initiated.

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It is now becoming possible to get reliable statistics about blindness. This has been made possible by the medical reports required by the Social Security Board. Even though such reports cover only the needy blind, a truer picture of the causes of blindness in this country will be secured. We may even hope in a few years to be getting adequate information concerning the incidence of blindness.

Statistical studies of the causes of blindness are of value only in proportion to the needs, faults and possible preventive and rehabilitative measures that they point out. There is no reason why blindness should not be a reportable condition — reportable to some official state agency as soon as it is established. There should exist in every state an official agency to which blindness in a person, young or old, rich or poor, is reported as it arises, thus giving a true picture of the incidence of blindness that is of more importance than the knowledge of the number of blind adults receiving assistance.

When the medical findings reveal that there is a reasonable chance of restoring sight, every endeavor should be made to persuade the applicant to have his sight restored.

One can say that the subject of blindness and its prevention has wide ramifications, the emphasis being placed in different states on the various phases of work. What is developed in the future will depend somewhat on how official and private agencies have been developed in the various states.

The Massachusetts Division of the Blind, concerned chiefly with the education and rehabilitation of the blind and with the care of the indigent blind, is now greatly concerned with the larger and more important program, the prevention of blindness. In this program, the responsibility rests not only on the ophthalmologist but on the entire medical profession. How well the medical profession performs and carries out the provision of the laws that aim primarily to prevent blindness will be one of the most important factors.

No one will argue that the use of prophylactic drops in newborn infants has not reduced blindness from ophthalmia neonatorum. Statistics have proved without a shadow of doubt that this is true. Within the past year not one case of a baby who was blinded because of this disease has been reported to the Division of the Blind. It becomes more important than ever to be vigilant in such cases, since it is a well-known fact that the incidence of venereal diseases increases in wartime. The law requires a Wassermann or Hinton test of pregnant women, making possible the treatment of syphilis when present in the early stages of pregnancy not only as a benefit to the mother, but also to prevent the birth of syphilitic offspring who may later develop interstitial keratitis, one of the chief causes of blindness. The law requiring a Wassermann or Hinton test before marriage has the same aim — to prevent the birth of a syphilitic offspring who may later become blind.

When it is realized that communicable diseases and trauma are two of the most important causes of blindness, we will doubtless all agree that something can be done to reduce the number of blind in this category.

It is of interest to note that conservation-of-vision committees of state medical societies have been appointed in the following states: Alabama, Connecticut, Florida, Indiana, Kansas, Maine, Missouri, Nebraska, New Hampshire, New Jersey, Oklahoma, Oregon, Pennsylvania, South Carolina and West Virginia. Special committees under state medical societies, also concerned with conservation of vision, have been appointed in the following states: Delaware, Georgia, Iowa, Minnesota, New Hampshire, South Dakota, Tennessee and Wisconsin. Plans are also under way for the publication of an article in the *West Virginia State Medical Journal* that will discuss industrial accidents, glaucoma, ophthalmia neonatorum and trachoma.

Eleven hundred and seventy-six cases of blindness now receiving aid in Massachusetts have been coded in accordance with the standard classification developed by the Committee on Statistics of the Blind, and the results show that there is need of the following: more care in reporting the etiologic factors of blindness; the early detection of all cases of glaucoma; the detection of diabetes before the devastating effects of this disease become manifest; better care of traumatic cases; and authentic data on hereditary cases.

It has been shown by this statistical study that the causes of blindness correspond in percentages closely to those of other states that have made a similar study.

The first principal cause to be considered is infectious disease, such as diphtheria, gonorrhea, measles, meningitis, ophthalmia of the newborn, scarlet fever, smallpox, syphilis, trachoma, tuberculosis and typhoid fever. Three hundred and seventy-six cases (32 per cent) were found in this category. Of these, 128 (11 per cent) were due to syphilis, 51 (5 per cent) to ophthalmia of the newborn, and 150 (13 per cent) to infectious diseases not specified. This percentage can be greatly reduced, since the effectiveness of chemotherapy has been so well established. It requires greater

vigilance on the part of physicians, and when necessary the seeking of advice from a competent ophthalmologist. By following this plan it should be possible to cut this percentage in half.

Next in importance is trauma. From this cause there were 61 cases, or slightly over 5 per cent. It is true that there will always be some cases of blindness due to trauma, but the present rate is altogether too high. It should be recognized that a perforating injury of an eye may not only cause the injured eye to be blind, but may so affect the other eye from sympathetic disease that the victim becomes totally blind. It is the duty of the medical profession to educate the public in regard to this threatened danger, and to see that such cases receive the care of a competent ophthalmologist. A study by Kerby* of 4739 children who are in schools for the blind in the United States shows that 374 cases were due to trauma, and that in 4 out of 10 of the injured cases blindness followed from development of sympathetic disease in the uninjured eye.

Ninety-three (8 per cent) of the 1176 cases of blindness were due to general diseases. This includes diabetes and hypertensive disease, including the arteriosclerotic degenerative diseases. It may not be possible to accomplish very much with hypertension and degenerations resulting from arteriosclerosis; nevertheless, the early recognition of diabetes is most important. It happens altogether too frequently that diabetes is not suspected until the patient has visual complaints, and when he is examined by his eye physician it is discovered that the underlying cause is diabetes. Such a person should certainly have had proper treatment long before he or she reached this stage, blindness thus being prevented.

It was necessary to classify 463 cases (40 per cent) as having an undetermined cause. This seems a rather high figure, and a more careful investigation and study of the cases might have revealed the etiology of the disease.

In 348 cases (30 per cent) the etiology was classified as unknown. This group included cases of glaucoma, cataract and myopia. In cataract sight is of course often restored by removal of the cataract. Regarding myopia, there seem to be no means at present of checking the progress of this condition. The fact that heredity is a factor in myopia should be recognized. Glaucoma was the cause of blindness in 119 cases (10 per cent). This is usually a symptomless disease of middle life, and is one that the ophthalmologist always has in mind when examining anyone who seeks his advice. Often there is no warning whatsoever of the disease, since the central visual acuity is lost only in the latest stages. The family physician is the first to be consulted by many so afflicted, and they depend on him for advice. He should be sufficiently acquainted with this disease to give them competent advice. Only a trained ophthalmologist can recognize this disease in its early stages. If this is done, proper treatment and care can avoid blindness.

In 152 cases (13 per cent) the blindness was of prenatal or hereditary origin. It seems to be a reflection on the medical profession that so large a number are blind from these causes. Apparently the only way that this number can be reduced is by educating the public of the danger of transmitting these conditions to their offspring.

This year the director of the Division of the Blind, with the co-operation of the Medical Advisory Committee, has had the following laws enacted in Massachusetts. First is an act relative to recording the treatment of infants at birth. This law requires the physician or hospital medical officer to treat the eyes of an infant within two hours after birth with a prophylactic remedy furnished or approved by the Department of Public Health, and he must record on the birth certificate the use of such a prophylactic. Whoever violates this section is punishable by a fine of not more than one hundred dollars. Second is an act relative to reports of treatment of certain wounds. This act classifies wounds from a BB gun or other air rifle with the firearm or gunshot wounds that must be reported to the Commissioner of Public Safety or to the police authorities of the town concerned. Third is a law making it mandatory to report all cases where the vision is 20/200 or less in the better eye or where the peripheral field of vision has contracted to a radius of 10° or less, regardless of visual acuity.

Prevention of blindness should be the chief interest of all official agencies for the blind and of all other agencies concerned with the welfare and health of the population. This program for the prevention of blindness cannot succeed without the full co-operation of the entire medical profession. There are certain fundamentals on which such prevention work must rest. These are an adequate medical determination of blindness, the early recognition of the potentially blind person, the ability to care for those potentially blind, whether adults or children, in an adequate manner, proper prenatal care, and a proper liaison between official agencies for the blind and other agencies, such as the departments of public health and of public safety, industrial commissions, labor commissions and departments of education.

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*Kerby, C. E. Eye conditions among pupils in schools for blind. *Outlook for the Blind* 36:270-276, 1942.

THE THERAPEUTIC VALUE OF TESTOSTERONE PROPIONATE IN ANGINA PECTORIS*

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ALTHOUGH an acute attack of angina pectoris is readily controlled with nitroglycerin, the treatment available for the prevention of such attacks is unsatisfactory. It has been observed than an increase in arterialization of cutaneous blood results when certain organic diseases of the peripheral blood vessels are treated with the testicular hormone, testosterone propionate.[1] There is also some experimental evidence that androgens and estrogens bring about vasodilatation.[2] With the hope, therefore, of improving the cardiac blood supply by increasing the collateral circulation or the degree of vasodilatation of the coronary arteries, or both, testosterone propionate has recently been used in the treatment of angina pectoris. Published reports thus far have been uniformly favorable.[3–7] The purpose of this paper is to record the results obtained with this form of therapy in an additional series of cases.

Nineteen patients, ranging in age from thirty-five to seventy years and presenting definite evidence of angina pectoris, were given tri-weekly injections of 25 mg. of testosterone propionate§ (Table 1). Eighteen were treated for four weeks, and 1 for seven weeks. Of the entire group, 16 were men. Nine patients had hypertension (a blood pressure of over 150/90 on repeated examinations). Three of these had a history of coronary thrombosis. Of 9 with normal blood pressures, 2 had had a previous infarction. The remaining case was that of a woman of thirty-nine with rheumatic aortic stenosis and insufficiency. The duration of angina pectoris ranged from one month to thirteen years, averaging six years. Each patient was accustomed to the use of nitroglycerin, and, with two exceptions, used a fairly constant number of pills a day. Reference to the daily nitroglycerin consumption offered some measure of the effectiveness of the therapy. The injections were generally given during the late fall and early winter months, so that observations were made during the time of the year when angina pectoris tends to become especially severe. This is important, for the interpretation of any therapeutic procedure carried out just before the advent of warm weather is always open to question. In all but 2 cases, no other medication was given concurrently and no change was made in the daily routine once treatment was begun.

Evaluation of the results was based on the patient's estimation of the amount of physical activity he was able to perform without precipitating an attack of pain, and the number of nitroglycerin tablets necessary over a twenty-four-hour period. These observations were recorded at the beginning of, during and at the conclusion of the injections. They were again noted from one to fifteen months later. The degree of improvement was classified as marked, moderate and questionable. When the patient was able to reduce the number of nitroglycerin tablets by two thirds or more, the improvement was considered to be marked. This result was always accompanied by an increased tolerance for physical activity. Moderate improvement was considered to have occurred when there was some, but not marked, reduction in the use of nitroglycerin. Those who reported that they felt somewhat better but were unable to do with a smaller number of pills or to increase their tolerance for effort were looked on as questionably improved.

Marked improvement was noted in 5 of the 19 patients. Two, however, reverted to their former clinical state within six to eight weeks, and 1, after a period of fifteen months, obtained no relief when a second series of injections became necessary. Of the remaining 2 patients, one maintained the improvement for four months, the other for one month. It is apparent, therefore, that of the 5 patients who experienced definite relief only 2 continued to benefit after four months, and in 1 of these the result could not be duplicated when it became necessary to repeat the therapy.

Moderate improvement was observed in 1 case, but aminophyllin was given with the testosterone, and it is also likely that a coronary occlusion took place just prior to medication. Questionable results were obtained in 2 patients, but even that degree of improvement was maintained by only one of them during the subsequent months. Death occurred in the other patient who, although temporarily somewhat improved, was also receiving digitalis and a mercury diuretic.

In 11 patients no change whatever was seen at the conclusion of treatment or at any time there-

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§The testosterone propionate used in this study was supplied by Ciba Pharmaceutical Products, Incorporated, Summit, New Jersey, under the trade name Perandren.

TABLE 1. *Summary of Data.*

Case	Age	Sex	Duration of Angina	Before Therapy: Limit of Physical Activity	Before Therapy: Nitroglycerin Pills Required Daily	Before Therapy: Blood Pressure	Before Therapy: Electrocardiogram
	yr.		yr.				
1	58	M	3	Pain after walking 100 feet on level ground; no pain at rest.	6–8	180/86	Normal
2	52	M	1/10	Pain after walking city block, also after shaving; no pain at rest.	6	180/100	Normal
3	65	M	9	Pain after walking 1 or 2 blocks; no pain at rest.	1–2	190/88	Normal
4	35	M	1/2	Pain when climbing stairs; no pain at rest.	3–4	110/80	Normal
5	54	F	1	Pain after walking half a block, also with emotional upsets; no pain at rest.	5–7	180/100	Normal
6	63	M	6	Semi-invalid because of pain with the slightest effort; no pain at rest.	5	138/76	Left bundle-branch block; T_1 and T_2 inverted.
7	63	M	10	Varying amount of effort resulted in pain; pain at rest occasionally.	4–8	210/120	Diphasic T_1 and T_2
8	39	F	2	Pain on little effort and at rest	3	130/70	T_1 inverted
9	50	M	6	Pain with effort and emotion and at rest	3	130/80	Diphasic T_1 and T_2
10	50	M	1/2	Pain with effort, after meals and at rest	2–3	196/126	Sharp inversion of T_1 and T_4
11	70	M	12	Pain with little effort; no pain at rest.	5–8	130/72	Right bundle-branch block
12	56	M	6	Pain with little effort and at rest	4–5	170/80	Intraventricular block; T_1, T_2 and T_4 inverted.
13	39	M	4	Pain on effort after meals	0	150/88	Normal
14	50	M	10	Pain after walking half a block.	1	130/78	T_1 sharply inverted
15	42	M	2	Pain on walking	5–6	118/78	Normal
16	60	M	13	Pain climbing stairs and at rest	2	135/80	Normal
17	66	M	12	Pain after walking half a block	2–3	126/80	Right bundle-branch block
18	55	M	7	Pain on walking up incline	1–2	220/110	Normal
19	40	M	6	Pain with varying types of effort	3–4	108/75	Normal

Case	After Therapy: Therapy Begun	Nitroglycerin Pills Required Daily	Blood Pressure	Follow-Up Period	Results
				mo.	
1	10/9/42	1–2	170/60	4	Marked improvement; original symptoms returned after 2 months.
2	11/13/42	6	200/120	4	No improvement
3	11/23/42	1–2	178/78	2	No improvement
4	12/4/42	3–4	110/80	3	Questionable improvement; felt better for 2 months.
5	12/9/42	5–7	200/100	3	Questionable improvement; continued to feel somewhat better.
6	1/14/43	0	140/60	3	Marked improvement; 1 month later developed pneumonia, after which original symptoms returned.
7	3/1/43	4–8	240/100	1	No improvement
8	3/15/43	3	128/78	1	No improvement
9	9/20/42	3	130/70	2	No improvement
10	3/22/43	1–2	190/120	2	Aminophyllin also given; coronary occlusion probably occurred just before therapy; moderate improvement for 1 month.
11	11/1/42	5–8	126/70	4	No improvement.
12	1/12/43	4–5	156/100	1	Died 1 month after treatment was finished
13	10/14/42	0	140/80	4	Marked improvement, which has been maintained
14	3/11/43	1	140/90	1	No improvement
15	8/1/42	1	120/70	1	Marked improvement
16	9/1/41 12/1/42	5–6	140/76	16	Marked improvement after first series; no improvement after second.
17	1/18/43	2–3	130/80	2	No improvement; coronary occlusion 2 months later.
18	3/10/43	1–2	210/110	1	No improvement
19	2/2/43	3–4	108/75	2	No improvement

after. One of these developed a coronary occlusion two months after the injections were completed.

No changes in the blood pressure or electrocardiogram were observed in any case and no toxic effects or significant changes in libido were noted. The behavior of this entire group was not unlike what would be expected in following any average series of cases of angina pectoris over a short period of time, one patient having died unexpectedly and another having developed an acute coronary thrombosis.

The difficulty of appraising therapy in the treatment of angina pectoris is perhaps best illustrated by the history of one of the patients in this group. Thirteen years ago, R. S., then forty-seven years of age, had been seen by one of us (S. A. L.) and diagnosed as having coronary artery disease and angina pectoris. At that time he could not walk a city block without experiencing the crushing substernal oppression so characteristic of angina. During the following twelve years, while receiving no specific form of therapy, there was considerable spontaneous improvement so that it was not unusual for the patient to walk miles without pain. Obviously this improvement could have been credited to any treatment used at the beginning of that period. Over a year ago, when the attacks of angina again became very frequent, testosterone was administered and considerable relief was noted. Recently, however, another course of injections failed to duplicate that result. May not this entire sequence of events reflect the vagaries of angina pectoris rather than the true effect of any therapeutic agent?

Summary

Testosterone propionate in doses of 25 mg. three times a week was given to 18 patients with typical angina pectoris for four weeks, and to 1 patient for seven weeks.

In all but 2 cases the patients received no other medication and continued the daily routine to which they had been accustomed.

Of the 19 patients, 9 were hypertensive and 1 had rheumatic aortic stenosis and insufficiency. Five had had a previous coronary occlusion.

Results were judged by the amount of physical activity necessary to produce an attack of angina, and the number of nitroglycerin tablets used daily. The degree of improvement was classified as marked, moderate and questionable.

Five were markedly improved at the conclusion of the treatment. Two, however, reverted to their former clinical state within six to eight weeks, 1 obtained no relief from a second series of injections after fifteen months of comparative comfort, and 1 has been followed for only one month. One patient was moderately improved, 2 questionably improved, and the remaining 11 obtained no benefit.

No change in the blood pressure or electrocardiogram and no toxic effects were noted.

Realizing that the clinical course of angina pectoris may vary a great deal spontaneously, we are unable to conclude that testosterone propionate has any beneficial therapeutic effect in this disease.

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THE TREATMENT OF RHEUMATOID ARTHRITIS WITH GOLD*

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ALTHOUGH the history of the use of gold salts in the treatment of rheumatoid arthritis is extremely interesting and unusual, it will not be recounted here since it has been so adequately summarized by Cecil and his collaborators.[1] It is interesting, however, to note that the use of gold in arthritis probably owes its origin to Mollgaard, who in 1927 thought that this precious metal had value in the treatment of tuberculosis. Some French students of arthritis believe that tuberculosis is the causative agent in the rheumatoid form of this disease, and this may well have suggested to Forestier[2] the use of gold salts in the treatment of arthritis.

Gold is unique also in that it is practically the only form of therapy among the many hundreds suggested for the treatment of arthritis that has had consistently favorable reports. The fact that it was slow to gain favor, particularly in this country, was due to the obvious toxic properties of the agent and its untoward effects. That these are still large factors seems to be evidenced by the facts submitted by all the writers on the subject and will be prominently emphasized in this report.

PHARMACOLOGY

This study has not brought to light any positive facts concerning the action of gold salts in alleviating the symptoms of rheumatoid arthritis. Whether its action is bacteriostatic,[3] shock-producing,[4] immunologic to joint structures[5] or stimulating to the reticuloendothelial system[6] still remains in the realm of theory.

Physiologic facts in respect to the fate of gold after injection into the human body are quite well established. Freyberg, Block and Levey[7] and Block, Buchanan and Freyberg[8] have shown that colloidal gold and colloidal gold sulfide are poorly absorbed and that more gold per gram of tissue is found in the liver than in the kidney, and have found that the feces are the chief route of excretion. In the case of crystalline preparations (gold sodium thiomalate, gold sodium thiosulfate and sodium succinimide aurate), more gold was found in the kidney per gram of tissue than in the liver, and during the time this preparation was used most of the gold was excreted in the urine.

Experimentally, the site of the primary pathologic lesions following the administration of these substances occurs in the organs where the greatest deposition of gold occurs.[9] That this is also the case in human beings seems to have been borne out clinically. Another feature of importance is the large percentage of gold salt that is retained in the organism for months before elimination is complete.[10]

GOLD PREPARATION AND METHOD OF THERAPY

The gold salts used in this study were limited exclusively to aurothioglucose,§ and the maximum dosage in any one course was 1.24 gm., given over a period of fifteen weeks. Ten-milligram, 25-mg. and 50-mg. doses were given intramuscularly semiweekly for two weeks each, and 100-mg. doses were given weekly for nine weeks. A second course was never begun until after a six-week period had elapsed. Many of the cases received two courses and some of them three. The second course was repeated no matter what the result had been after the first, unless there had been untoward effects or reactions contraindicating such a procedure.

CLINICAL MATERIAL

The type of case used in this series was to a large extent governed by the type of patient attending the clinics from which the material was obtained. The Arthritis Clinic of the Philadelphia General Hospital derives the greatest part of its case load from indigent chronic patients who have had the disease for some time and have made the rounds of hospitals. This is also true, to a great extent, of the clinic at the Jefferson Hospital, although a great number of patients are referred there by physicians. The latter patients may be on an economic scale slightly above that of the patients of the Philadelphia General Hospital clinic, but the type of case does not appear to differ a great deal. Thus most of the cases were far advanced (Table 1) and had received at some time or other throughout the course of their disease all types of treatment.

The usual study consisted of a complete physical examination, including a complete blood count, urinalysis, and determination of the sedimentation rate (Westegren), as a routine. Other studies were done as indicated. Further sedimentation rate determinations were made at the termination of each course of treatment and before the beginning of the next. Weekly blood-cell counts and

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§Aurothioglucose in the form of Solganol-B Oleosum was supplied by the Schering Corporation, Bloomfield, New Jersey, through the courtesy of Dr. William H. Stoner.

urinalyses were done. There is no description of the urinary findings, since the reports were almost invariably negative. Occasionally a transient albuminuria was noted, but otherwise there was little of significance.

TABLE 1. *Duration of Disease at the Beginning of Treatment.*

DURATION	NO. OF CASES	PER CENT
Under 1 year	8	6
1 year	30	25
2–4 years	28	23
5–9 years	32	26
10 years or over	24	20
Total	122	

One patient developed a leukopenia (a white-cell count below 4000), and the fact that after treatment was stopped and liver extract administered intramuscularly a complete recovery ensued made routine blood-cell counts worth the effort. There was no appreciable change in the hemoglobin level or the red cell count. Many hundreds of determinations were made.

In all the cases an increased sedimentation time was a prerequisite for gold therapy (Table 2).

TABLE 2. *Sedimentation Rates at the Beginning of Treatment.*

SEDIMENTATION RATES	NO. OF CASES
mm./hr.	
Below 9	0
9–15	5
16–20	5
21–30	29
31–40	20
41–50	10
51–60	14
61–70	5
71–80	4
81–90	5
91–100	14
101 or over	11
Total	122

With the use of the Westegren method, 8 mm. per hour was considered as the upper limit of normal.

All the cases were polyarticular. Two showed spondylitis deformans. To the student of this disease it will be quite obvious that one rarely finds rheumatoid arthritis involving but one joint and at the same time fulfilling all the necessary criteria for diagnosis.

The cases were grouped according to a functional classification that has been used in our clinics for some time in the study of arthritic patients. It is as follows:

Class 1. Patients presenting the subjective picture characteristic of atrophic arthritis, with duration less than six months and with no demonstrable changes in the joints by clinical or roentgenologic examination.

Patients presenting the subjective picture characteristic of atrophic arthritis, with duration less than one year and joint changes demonstrable but of a moderate degree. There is usually complete subsidence following the removal of foci and adequate therapy.

Class 2. Patients with typical joint changes in one or more groups of joints. The changes are more or less permanent in character but of such a nature that activity is only slightly limited.

Class 3. Patients in whom joint changes have advanced to such a degree that physical activity is greatly limited.

Class 4. Patients with joint changes of such a nature that dislocations, ankyloses and contractures cause total disability. The patient must of necessity be confined to a wheel chair or to bed.

With this classification in mind, it will be noted that only cases of rheumatoid arthritis were included in this study. Hypertrophic arthritis was not considered. The distribution of grades by ages is shown in Table 3.

TABLE 3. *Grade of Disease According to Age.*

AGE	CLASS 1	CLASS 2	CLASS 3	CLASS 4	TOTALS
yr.					
1–20	0	1	1	0	2
21–30	0	5	8	0	13
31–40	1	2	17	1	21
41–50	0	6	24	1	31
51–60	0	8	25	3	36
61–70	0	1	6	10	17
Over 70	0	0	1	1	2
Totals	1	23	82	16	122
Percentages	1	19	67	13	

TOXIC REACTIONS

The following is a list of untoward reactions reported as due to gold therapy.[11]

Skin:
- Erythema
- Exanthema
- Papular eruption
- Desquamation
- Morbilliform rashes
- Urticaria
- Exfoliative dermatitis

Eyes:
- Conjunctivitis

Mouth:
- Metallic taste
- Anesthesia of tongue
- Transient loss of taste
- Dysphagia
- Sore tongue and gums
- Ulcerative stomatitis

Genitourinary tract:
- Weight loss
- Nausea
- Vomiting
- Epigastric distress
- Diarrhea

Liver:
- Hepatitis
- Jaundice
- Acute yellow atrophy

Respiratory tract:
- Cough (gold bronchitis)

Kidneys:
- Mild transient albuminuria
- Uremia

Central nervous system:
- Eighth-nerve deafness

Hematopoietic system:
- Epistaxis
- Purpura hemorrhagica
- Aplastic anemia
- Agranulocytosis

Hartfall and Garland[12] reported 45 per cent toxic reactions in 100 cases. Later Hartfall et al.[13] reported 900 cases with 52.5 per cent toxic reactions. Crawford[14] treated 27 cases with 44 per cent untoward reactions. Sashin and Spanbock[15] had 18 per cent toxic reactions in 22 cases, and Parr and Shipton[16] 26 per cent in 70 cases, Key et al.[17] 63 per cent in 44 cases, Snyder et al.[18] 15 per cent in 145 cases, and Ellman et al.[19] 27 per cent in 90 cases.

One cannot doubt that gold therapy is dangerous in the hands of the average physician when one glances at the long list of untoward reactions that have been reported in the literature. Much of this, however, is avoidable when reasonable care is taken. The purpose of this study is not only to add to the already long list of statistics, but to contribute what is believed to be a simple method to reduce the incidence of untoward reactions. It has been suggested that large amounts of vitamin C be used.[20] It is, however, agreed that there is no scientific basis for this except perhaps that since most of the untoward reactions are reflected in the skin and mucous membranes, it might be wise to attempt to decrease the capillary permeability with vitamin C. Therefore as adjuncts to the gold therapy, the patient was instructed to take 16 ounces of fruit juices as well as a minimum of ¼ pound of liver three times weekly. Any unusual signs or symptoms that might develop between visits were to be reported. The patient was especially warned to report itching of the skin, sore mouth or rash, regardless of severity.

Untoward reactions regardless of severity or whether or not attributable to gold were cause for interruption of treatment. Frequently, treatment was again begun when the reaction subsided. Reactions were treated by intramuscular injections of 4 units of crude liver extract three times weekly.

In Table 4 are listed the untoward reactions encountered in this study. In the group of 122 cases that received but one course of gold therapy, reactions occurred in 12 cases (9.8 per cent). In the 38 cases receiving two courses, 7 (18 per cent) had reactions, and in the 16 cases receiving three courses, 1 case (6 per cent) had a reaction. Thus in one hundred and seventy-six series of injections, reactions occurred in 20 cases. The table also shows the total dose of aurothioglucose received when the reaction became manifest.

TABLE 4. *Untoward Reactions.*

	Reaction	Dose
		mg.
One course:		
	Generalized pruritus and stomatitis	940
	Maxillary parotitis	290
	Leukopenia to below 5000 white cells	240
	Generalized urticaria	190
	Pruritus	740
	Generalized papular pruritic lesion	640
	Macular dermatitis	840
	Macular dermatitis with scaly centers	440
	Urticaria	290
	Pruritus	340
	Stomatitis	140
	Pruritus with macular eruption	290
Two courses:		
	Stomatitis	940*
	Severe eczema	140
	Hepatitis and jaundice	240
	Pityriasis rosacea	940
	Dermatitis of nose, chest and ears	640
	Ulcerative lesion of anterior pillar of left tonsil	505
	Pruritus	340
Three courses:		
	Seborrheic dermatitis	90†

*Plus 1240 mg. (first course).
†Plus 2480 mg. (first and second courses).

Results of Therapy

The results of any therapy employed in the treatment of arthritis are always extremely difficult to evaluate. The student of the disease is frequently hard pressed to classify results in the single case. Factors that create this situation are the wide variance in susceptibility to pain and discomfort, the patient's psychic response to having someone take an interest in his plight and the resulting euphoria of some patients when under this influence. One must also consider the inherent tendency of rheumatoid arthritis to have natural remissions. All these must be dealt with and kept in mind when trying to evaluate results. In this study a simple classification of improvement has been attempted, and the cases have been divided as follows:

Group 1. No change: No response whatsoever.

Group 2. Improved: Few if any objective changes but definite subjective improvement evidenced by the patient.

Group 3. Markedly improved: Both subjective and objective improvement; diminution of swelling and pain and ability to raise the arms above the head or to walk with or without aid.

Group 4. Very markedly improved: Marked diminution or complete relief of all subjective and objective symptoms. In some of these cases there remain some stiffness and soreness.

From the tables it appears that there was improvement of a sort in 87 per cent of the cases. If one were to consider the improvement in Group 2 as of questionable nature, since the patient's own statements were the only guide, there remain 53 per cent that were benefited by this form of therapy.

As has been reported by others, there was generally a reduction in the sedimentation rate. Table

5 shows that 78 per cent of those patients receiving one course of treatment manifested a reduction in sedimentation rate. A reduction was noted in 47 per cent of those patients receiving a second course and in 62 per cent of those receiving the third course. At the end of the first course of gold 7 per cent of the patients showed an increase in sedimentation rate. In spite of this, many of the patients were improved.

Whether or not the gradual reduction in sedimentation rate has any bearing on the rate of improvement one cannot say. However, it would seem so until one examines those patients whose sedimentation rate showed no change or was even increased at the end of a course of treatment, when one finds that improvement existed without favorable change in this test.

Table 6 shows the sedimentation rates before and after treatment in the 38 cases receiving two or three courses of treatment.

Table 7 lists the therapeutic results according to the duration of the disease. It will be noted that in the majority of cases the disease existed for more than one year. Almost 70 per cent of the patients were afflicted for more than two years and 45 per cent for more than five years. This series consisted of only 8 patients with rheumatoid arthritis of less than one year's duration. Although the improvement in these cases was marked, the series is not large enough to agree with the finding of other investigators that the earlier the case, the better is the prospect of recovery. Twenty-four patients suffered for more than ten years. Of these, 33 per cent showed subjective improvement, 25 per cent were markedly improved, and 25 per cent were very markedly improved after one course of treatment. Two cases showed no change and 2 were actually worse. These findings are extremely significant in view of the average opinion among physicians that cases of this type should be considered hopeless. Whenever rheumatoid arthritis exists, even for many years, if pain is still present and the sedimentation rate is elevated, the patient should be given the benefit of gold therapy. If the result can only be classified as "improved," it will have been worth the effort.

Table 8 lists the results of treatment according to age groups. The majority of patients ranged between thirty-one and sixty years of age. It will be noticed that the age of the patient was no contraindication to treatment with gold, since the re-

TABLE 5. *Results of Treatment According to Changes in Sedimentation Rate.*

Therapeutic Result	Rate Reduced to Normal				Rate Reduced 50 Per Cent or More				Rate Reduced Less Than 50 Per Cent				Rate Unchanged				Rate Increased				All Cases	
	I*	II	III	TOTAL	I	II	III	TOTAL	I	II	III	TOTAL	I	II	III	TOTAL	I	II	III	TOTAL	NO.	PER CENT
Group 4 (V. M. I.)	6	1	0	7	21	4	1	26	14	2	1	17	6	1	0	7	3	3	0	6	63	36
Group 3 (M. I.)	0	1	1	2	6	2	0	8	9	0	2	11	1	1	1	3	1	4	1	6	30	17
Group 2 (I.)	3	0	1	4	13	2	1	16	19	4	0	23	7	2	1	10	3	4	1	8	61	35
Group 1 (N. C.)	0	0	0	0	0	1	1	2	3	0	2	5	2	0	1	3	1	3	1	5	15	9
Worse	0	0	0	0	0	1	0	1	2	0	0	2	2	0	0	2	0	2	0	2	7	4
Totals	9	2	2	13	40	10	3	53	47	6	5	58	18	4	3	25	8	16	3	27	176	
Percentages†	7	5	12		33	26	19		38	16	31		15	11	19		7	42	19			

*Roman numerals refer to courses.
†Of total in any one course.

TABLE 6. *Sedimentation Rates before and after in 38 Patients Receiving Two or More Courses of Therapy.*

Case No.	Course I			Course II			Course III		
	Before	After	Results	Before	After	Results	Before	After	Results
1	34	12	V. M. I.*	14	12	I.			
2	64	41	I.	47	80	N. C.	86	80	N. C.
3	75	15	M. I.	15	15	I.			
4	58	10	V. M. I.	50	78	I.	65	54	N. C.
5	95	75	I.	70	75	W.			
6	26	16	I.	16	31	W.			
7	36	16	V. M. I.	13	13	M. I.	18	32	N. C.
8	53	30	M. I.	10	37	N. C.			
9	50	31	V. M. I.	37	18	V. M. I.			
10	38	2	V. M. I.	45	70	V. M. I.			
11	60	10	I.	32	15	I.			
12	60	18	V. M. I.	25	15	V. M. I.			
13	50	50	V. M. I.	30	10	V. M. I.			
14	28	40	V. M. I.	45	29	V. M. I.	37	30	V. M. I.
15	95	40	V. M. I.	85	75	I.	88	85	N. C.
16	40	28	M. I.	40	38	V. M. I.			
17	70	35	I.	35	13	V. M. I.			
18	35	18	V. M. I.	16	8	V. M. I.			
19	115	69	V. M. I.	70	35	V. M. I.			
20	100	70	V. M. I.	70	31	V. M. I.			
21	35	16	I.	17	10	I.	53	37	M. I.
22	28	27	I.	55	120	I.	105	106	M. I.
23	43	28	M. I.	27	100	W.	90	65	N. C.
24	10	10	I.	55	20	I.	25	20	M. I.
25	24	14	I.	9	20	I.			
26	30	23	M. I.	23	30	I.			
27	22	10	V. M. I.	10	18	V. M. I.			
28	25	23	I.	26	38	I.	18	105	M. I.
29	19	14	M. I.	10	90	V. M. I.	19	13	M. I.
30	28	55	V. M. I.	70	100	M. I.			
31	88	25	I.	85	25	I.			
32	75	55	M. I.	5	15	M. I.	59	16	M. I.
33	27	40	I.	20	112	N. C.	9	2	I.
34	40	20	I.	30	25	I.	43	20	V. M. I.
35	17	10	I.	6	40	M. I.			
36	45	15	M. I.	7	44	M. I.			
37	50	20	V. M. I.	37	18	I.	70	35	I.
38	95	90	I.	28	100	M. I.	112	110	I.

*The abbreviations correspond to those used in Table 5.

sults obtained were essentially the same as those in the younger age groups.

Comment

In our experience in two large arthritis clinics over a period of more than fifteen years, no form of therapy has been encountered that offers so much promise in the treatment of rheumatoid arthritis as does gold therapy. Many of the cases presented have been treated in these clinics and elsewhere for many years without benefit, the therapy consisting of removal of foci of infection, courses of gold therapy. It is likewise borne out that more than one course of treatment is necessary to maintain relief. However, not so much improvement should be expected from subsequent courses of treatment as one is apt to get from the first one.

Ignoring those cases that showed only subjective improvement, 54 per cent of those receiving one course and 53 per cent of those receiving three courses showed both subjective and objective improvement.

The incidence of 9.8 per cent of untoward reactions in individuals receiving but one course of treatment is significantly lower than that reported by other authors. However, the incidence was twice as great in those receiving two courses, but there was only 1 such case in these 16 patients receiving three courses. The grand total of 11 per cent of untoward reactions in 176 courses of gold therapy. It is likewise borne out that more than one course of treatment is necessary to maintain relief. However, not so much improvement should be expected from subsequent courses of treatment as one is apt to get from the first one.

Table 7. *Results of Treatment According to Duration of Disease.*

Therapeutic Result	Duration under 1 Yr.				Duration 1 Yr.				Duration 2–4 Yr.				Duration 5–9 Yr.				Duration 10 Yr. or Over				All Cases	
	I*	II	III	TOTAL	I	II	III	TOTAL	I	II	III	TOTAL	I	II	III	TOTAL	I	II	III	TOTAL	NO.	PER CENT
Group 4 (V. M. I.)	4	0	0	4	18	4	0	22	8	1	0	9	14	5	2	21	6	1	0	7	63	36
Group 3 (M. I.)	1	1	0	2	3	4	2	9	5	2	1	8	2	1	2	5	6	0	0	6	30	17
Group 2 (I.)	3	0	0	3	8	3	1	12	12	3	3	18	14	2	0	16	8	4	0	12	61	35
Group 1 (N. C.)	0	0	0	0	1	1	0	2	2	0	1	3	1	1	3	5	2	2	1	5	15	9
Worse	0	0	0	0	0	0	0	0	1	1	0	2	1	1	0	2	2	1	0	3	7	4
Totals	8	1	0	9	30	12	3	45	28	7	5	40	32	10	7	49	24	8	1	33	176	
Percentages†	7	3	0		25	32	19		23	19	31		26	26	44		19	21	6			

*Roman numerals refer to courses.
†Of total in any one course.

Table 8. *Results of Treatment According to Age of Patient.*

Therapeutic Result	Less Than 21 Yr.				21–30 Yr.				31–40 Yr.				41–50 Yr.			
	I*	II	III	TOTAL	I	II	III	TOTAL	I	II	III	TOTAL	I	II	III	TOTAL
Group 4 (V. M. I.)	1	0	0	1	7	3	0	10	8	0	1	9	11	4	1	16
Group 3 (M. I.)	0	0	0	0	0	1	0	1	2	2	3	7	5	0	0	5
Group 2 (I.)	1	0	0	1	5	0	2	7	9	2	0	11	12	7	2	21
Group 1 (N. C.)	0	0	0	0	1	0	0	1	2	2	2	6	2	0	0	2
Worse	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	2
Totals	2	0	0	2	13	4	2	19	21	6	6	33	31	12	3	46
Percentages†	2	0	0		11	11	12		17	16	38		25	32	19	

	51–60 Yr.				61–70 Yr.				Over 70 Yr.				All Cases	
	I	II	III	TOTAL	I	II	III	TOTAL	I	II	III	TOTAL	NO.	PER CENT
Group 4 (V. M. I.)	17	4	0	21	4	1	0	5	1	0	0	1	63	36
Group 3 (M. I.)	8	2	2	12	4	1	0	5	0	0	0	0	30	17
Group 2 (I.)	8	3	0	11	6	0	0	6	1	2	1	4	61	35
Group 1 (N. C.)	1	0	2	3	2	1	0	3	0	0	0	0	15	9
Worse	2	2	0	4	1	0	0	1	0	0	0	0	7	4
Totals	36	11	4	51	17	3	0	20	2	2	1	5	176	
Percentages†	30	29	25		14	8	0		2	5	6			

*Roman numerals refer to courses.
†Of total in any one course.

vaccines, filtrates, snake venom, sulfur, vitamins, physiotherapy, artificial fever and so forth.

As has been reported by other writers, there is a decided tendency toward a reduction in the sedimentation time — 78 per cent of 122 cases receiving one course, 47 per cent of those receiving two courses, and 62 per cent of those receiving three

therapy suggests a distinct reduction in the incidence noted by other investigators. With but one exception, reactions were not manifested until the patient had received at least the 50-mg. doses. When it is considered that 100 mg. has been advocated as an initial dose, it is understandable that a greater incidence of untoward reactions might occur. In this study, three factors are thought to have been responsible for the reduction of toxic reactions: namely, the use of large doses of fruit juices for vitamin C, the use of liver for vitamin B complex and extreme caution in the consideration of untoward reactions.

Age does not appear to be a contraindication to gold therapy. Significant changes in the blood were observed in only 1 case. Likewise, there were no important changes in the urine.

Summary

A series of 122 patients receiving a total of one hundred and seventy-six courses of 1.24 gm. of aurothioglucose intramuscularly is reported.

The results of all courses of treatment were as follows:

Thirty-five per cent showed only subjective improvement, 17 per cent were much improved, 36 per cent were very much improved, 9 per cent showed no change, and 4 per cent were worse.

The percentage of untoward reactions was 9.8 per cent during the first course, 18 per cent during the second, and 6 per cent during the third, an incidence of 11 per cent in one hundred and seventy-six courses of therapy.

A simple method for the reduction of untoward reactions is suggested.

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MEDICAL PROGRESS

THE PLASMA PROTEINS: THEIR IMPORTANCE IN CLINICAL MEDICINE AND SURGERY (Concluded)*

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Clotting process. Fibrinogen is classified as a plasma globulin and is the soluble precursor of fibrin, which makes up the matrix of a blood clot. The fibrinogen molecule has properties that make for elasticity and a firm clot. It is a long, slender molecule exhibiting double refraction of flow.[2] Its source is in all probability the liver, but it can apparently be manufactured with such rapidity that only overwhelming hepatic damage will lead to a deficiency of plasma fibrinogen. This is occasionally seen in acute yellow atrophy and in carbon tetrachloride poisoning. A few cases of congenital fibrinogenopenia have been described.[59] Such deficiencies of fibrinogen are of little clinical significance because of their rarity.

On the other hand, two other globulins concerned with the clotting process are of great clinical importance, as recent work has shown. The first, prothrombin, is the precursor of thrombin, which, according to the classic clotting theory, is produced from prothrombin by the influence of calcium and thromboplastin derived from tissue juice or the breakdown of blood platelets. Prothrombin and thrombin apparently have the mobilities of beta globulins. Prothrombin is present in the circulation in considerable amounts under ordinary circumstances, but a marked fall in plasma prothrombin concentration occurs under certain clinical conditions, notably severe hepatic damage and severe obstructive jaundice. In the first case, the hypoprothrombinemia is apparently due to the failure of the liver to synthesize this protein[60] (it should be noted that the liver is again implicated); in the second case, the deficiency is not due to a primary failure in synthesis but to a failure of absorption of fat-soluble substances in general, of which vitamin K is one.[61] Vitamin K is apparently essential to the synthesis of prothrombin by the liver.[62] If it is injected or given by mouth with bile salts to promote its absorption, there is a prompt restoration of the blood-prothrombin level if hepatic function is adequate.[63] These discoveries are of great importance in biliary surgery, since one of the chief hazards of operations on cases of severe obstructive jaundice in the past was abnormal bleeding. In addition, the recognition of hypoprothrombinemia in cases of hemorrhagic disease of the newborn,[64] which may be prevented in some cases by the administration of vitamin K to the mother before delivery, is another important practical advance.[65]

Since clinicians are interested not only in treating defective clotting but also in producing controlled defects in clotting, the work on dicoumarin[66, 67] should be followed with interest. The use of this powerful drug, which seems to act specifically on prothrombin, in the treatment of thrombosis, has been delayed by the lack of suitable means of controlling the clotting defect once it is initiated. Hence, Davidson and MacDonald's[68] paper on the effectiveness of synthetic vitamin K_1 oxide in dicoumarin hypoprothrombinemia will be of great importance if further studies confirm their work.

The second globulin important in blood coagulation has been brought to light by the work of Tagnon, Taylor, Lozner and their associates. Nolf originally proposed that clotting is brought about by a proteolytic enzyme in the plasma that can produce clotting, or when present in larger amounts, lysis of clots.‡ Such an enzyme may be produced from plasma by treating it with chloroform. In addition to Nolf's work, which has been confirmed by Tagnon and his coworkers,[70, 71] Taylor and his associates[72] have for some years been interested in the substance that is deficient in hemophilic blood. This thromboplastic substance is definitely a globulin,[73] but its more accurate chemical characterization has not yet been carried out. This substance disappears fairly rapidly from hemophilic blood after administration, but it can be injected either in purified form or as fresh plasma, and temporarily rectifies the clotting defect of hemophilic plasma. It is of great interest that chloroform treatment of the globulin fraction, which rectifies the hemophilic coagulation defect, gives rise to a proteolytic enzyme.[74]

The articles in the medical-progress series of 1941 have been published in book form (*Medical Progress Annual*. Volume III. 678 pp. Springfield, Illinois: Charles C Thomas, 1942. $5.00).

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‡For those interested in the complexities of blood coagulation and in the evidence for Nolf's interpretation of the experimental data, his review[69] is recommended.

Catalytic agents. As Salter[75] has recently pointed out, many of the most physiologically active and important substances are of a catalytic nature, and hence are present in very small amounts in the blood. Enzymes and hormones fall into this group. Chemical research has indicated that most enzymes are of protein nature, with prosthetic groups that confer on them their special properties. Minute but measurable amounts of certain enzymes such as amylase, alkaline and acid phosphatase circulate normally in the plasma. Marked increases in concentration have been found to characterize certain pathologic conditions, such as the rise in serum amylase that is found in acute pancreatitis.[76] The hormones, derived from the pituitary and thyroid glands, are likewise active agents present in minute amounts, probably in the globulin fraction of the plasma. None of these substances are ordinarily considered with the plasma proteins, but their presence in plasma is pointed out to emphasize its complexity.

Pressor substances. In recent years it has become apparent that, in addition to the elevation of blood pressure produced by adrenalin in emergencies, another humoral mechanism exists that can elevate blood pressure in response to renal ischemia.[77] This field has been confused by the fact that the two chief groups of workers have introduced different terminologies. However, the fundamental facts are these. Renin, an enzyme and probably a globulin, is liberated from the kidney under various conditions that produce renal ischemia. It does not itself elevate blood pressure, but acts on a substrate ("hypertensinogen"[78] or "renin activator"[79]), which is one of the plasma globulins, to produce the true pressor substance ("hypertensin"[78] or "angiotonin"[79]), which is probably a polypeptide. Although this humoral mechanism of hypertension has not been demonstrated in cases of human hypertension, it seems likely that it may explain those cases of hypertension that are definitely due to renal disease. Hypertensin or angiotonin has a number of interesting physiologic effects on the circulation that are under active investigation.[80]

Abnormal globulins and hyperglobulinemia. A number of disease states are characterized by an increase in the globulin fraction of the plasma. The normal value for plasma globulin is from 2.0 to 2.5 gm. per 100 cc., and in some diseases this may rise as high as 6 or 7 gm. In many cases, but not always, this hyperglobulinemia is associated with hypoalbuminemia, so that the total protein value is a resultant of the two tendencies. Hyperglobulinemia may be due to an increase in the normal globulin constituents of the plasma, to the presence of abnormal globulins or to both. Gutman and his colleagues[81] have made a careful study of the plasma proteins in multiple myeloma, a disease characterized by extremely high plasma protein levels, and have shown that some cases are characterized by increases in different fractions of the normal serum globulins and some by abnormal globulins, one of which is the Bence-Jones protein, which appears in the urine and is characterized by its peculiar solubility behavior when heated. In addition to multiple myeloma, certain types of liver disease, particularly cirrhosis of the liver, are associated with hyperglobulinemia and the presence of abnormal globulins, and a number of chronic infectious diseases likewise manifest hyperglobulinemia. Of these, the commonest are the tropical diseases, particularly kala azar and chronic malaria; the chronic relapsing diseases thought to be due to allergy, such as acute nephritis, rheumatic fever, disseminated lupus erythematosus, periarteritis nodosa and dermatomyositis; lymphopathia venereum, which exhibits strikingly high plasma globulin levels; and a number of other chronic infectious diseases, such as subacute bacterial endocarditis and tuberculosis.[81]

Acute nonspecific responses to infection. One of the most interesting fields for speculation and study on the role of the plasma proteins is the response of the body to acute infection. The studies of Tillett, Francis, Avery, Abernethy and others have shown that there is a chemical fraction of the pneumococcus, the so-called "C carbohydrate," to which a group of rather peculiar immune reactions can be demonstrated in many acute infections, not necessarily pneumococcal in nature. Anti-C substance precipitins appear in the serum shortly after the onset of pneumonia and other acute infectious diseases, and disappear soon after recovery, unlike most antibodies that are specific and appear only after recovery. These antibodies manifest themselves by the appearance of a positive skin reaction to the C substance, which is intermediate between the immediate and delayed types, reaching its maximum in about eight hours.[82,83] They differ from ordinary antibodies also in that precipitation of the C substance takes place only in the presence of calcium ions.[84] Further studies of this peculiar antibody have shown that, unlike other antibodies that are normally found in the gamma globulin fraction, it seems to be present in the alpha globulin fraction,[85] a fraction of serum that has been shown by Longsworth and his colleagues[86] to increase during the acute stage of acute infectious diseases. Furthermore, it has been shown by immunologic methods to be a protein not present in normal serum.[87]

Possibly related to this interesting alpha globulin is the discovery of Tillett[88] that any febrile illness results in a rapid increase in the bactericidal power of the patient's serum for certain strains of beta-hemolytic streptococci, and that this bactericidal power disappears shortly after the subsidence of acute symptoms. This bactericidal property of the serum has been shown by Tillett and Stock[89] to be associated with a globulin fraction. Of equal interest is Menkin's[90, 91] recent discovery of the leukocytosis-promoting factor, which can be detected in the serum of animals with acute abscesses and can be concentrated from inflammatory exudates derived from animals and human beings. This factor is likewise a globulin,[92] and its connection with the other responses to acute infection is one that invites speculation and further study.

Undoubtedly this catalogue of the physiologic significance of the various globulins present in normal and pathologic human plasma is far from complete, but it serves to illustrate the complexity of plasma. Just as changes in the albumin fraction, and to a much lesser extent in the globulin fraction, reflect changes in the state of protein nutrition of the body, so changes in the amounts of the various globulins reflect changes in the constantly shifting equilibrium of the organism with its environment, changes which, although recognized by alterations in the plasma, are fundamentally due to alterations in the activities of different groups of tissues and cells.

Treatment of Disturbances of the Plasma Proteins

It should be clear from the foregoing discussion that alterations in the normal pattern of the plasma proteins are not diseases in themselves, but are merely reflections of more deep-seated changes in the body tissues. Therefore, treatment in most cases is not directed at the plasma protein disturbance itself, but at the underlying disease, except where alterations in the plasma, such as the hypoproteinemia of nephrosis, affect the whole organism adversely.

Hyperproteinemia

Hyperproteinemia, which is almost always hyperglobulinemia, is associated with diverse clinical conditions, the etiology of many of which is unknown, but for certain of which, such as kala azar, malaria and lymphopathia venereum, there are definite methods of treatment. Since hyperproteinemia per se has not yet been demonstrated to be harmful, its treatment at present would be unnecessary, even if the proper procedure were known. In a disease like hyperthyroidism the metabolic disturbances are related to the overproduction of thyroid hormone, which is circulating in the plasma. The absolute amounts of hormone, however, are so small, since it acts as a catalytic agent, that one does not think of hyperthyroidism as a specific type of hyperglobulinemia to be treated by suppression or removal of the organ giving rise to the globulin.

Hypoproteinemia

In contrast to excesses, deficiencies of the many plasma proteins are amenable to treatment, which is frequently required to correct serious disturbances of the body economy as a result of the deficiency of circulating protein itself or the underlying functional defect that it reflects. Two general lines of therapy are open to the physician: first, substitution or replacement therapy; and second, provision of adequate protein-forming materials or the stimulus to synthesis, thereby enabling the body to repair its own deficiency. The latter method is always preferable wherever possible, since it offers permanent rather than temporary relief. It takes time, however, and depends on the integrity of the synthetic processes, so that in acute emergencies, or where there is failure of synthesis, replacement therapy must be used.

A deficiency of *circulating total protein* is associated with the rapid loss of blood or plasma, such as occurs in hemorrhage, severe injuries and burns, although the *plasma protein concentration* and distribution may be normal. If the total amount of blood or plasma lost is so great that compensatory vasoconstriction is ineffective in maintaining the peripheral circulation, there occurs the marked fall in blood pressure characteristic of severe shock. Such a condition should be anticipated and prevented if possible by replacement therapy before collapse occurs. The capacity of the body to compensate for blood or plasma loss is conditioned by its ability to manufacture new plasma protein. This occurs at a remarkably rapid rate, provided an adequate circulation is maintained. Following a venesection of 15 to 20 per cent of the total blood volume a normal subject can replace the lost blood with new plasma in about three days.[93] Obviously, this is too slow to bring about recovery in traumatic shock, which may become irreversible in a few hours, and furthermore, it has been shown that plasma protein production in dogs is practically nil when the blood pressure is at shock levels.[94] It is because of this vicious circle that the early treatment of shock with fluids capable of maintaining blood volume is so important. Crystalloid solutions are too rapidly lost from the circulation and tend to lower the plasma protein concentration by dilution and by increasing the rate of plasma loss at the site of injury.[95] Foreign colloids, such as acacia,[96]

pectin[97] and gelatin,[98] have been used successfully to improve the circulation in such emergencies. The ideal replacement fluid, however, is that which most closely approximates that which is being lost. Thus, whole blood or a mixture of whole blood and plasma are best for wounds combining hemorrhage and trauma, whereas plasma is superior for crushing injuries, peritonitis and burns, where the factor of hemorrhage is minimal. Since the blood has a wide margin of safety in its oxygen-carrying capacity, it is usually possible to substitute plasma for blood for the sake of convenience in the emergency treatment of shock. This is the basis for the Red Cross Army-Navy dried plasma program, which provides a therapeutic agent that can be transported in the field without refrigeration and administered without cross matching. Since the effectiveness of plasma in restoring blood volume depends chiefly on its albumin content, the administration of sufficient albumin should be as efficacious as plasma in most shock cases. Because albumin is extremely soluble and stable it has been put up in concentrated form — 25 gm. in 100 cc. of saline — to provide an instantly available, compact blood substitute for emergency use under military conditions, where space is at a premium.[19] In clinical trials this has been shown to be effective,[99] but since it draws on the tissue fluids to increase the volume of circulating plasma, additional water and salt must sooner or later be given the patient by some route (per os, per rectum or parenterally), particularly in cases in which dehydration is present.

Hypoalbuminemia

Hypoalbuminemia, or a diminution of the albumin concentration below normal, gives rise to edema when the value for plasma albumin falls below 2.0 to 2.5 gm. per 100 cc., and is known to be associated with poor healing of surgical wounds, and even with wound disruption after operation.[100, 101] Hypoalbuminemia is a manifestation of a poor state of nutrition of the tissues in general. Thus, the maintenance of an adequate level of serum albumin is undoubtedly of equal importance in the treatment of medical and of surgical patients. The causes of hypoalbuminemia are excessive loss of albumin, such as occurs in nephrosis or repeated tappings, excessive utilization, as in febrile illness, and inadequate production due to poor protein intake, poor absorption or failure of albumin synthesis. Any one or a combination of these factors may operate in any particular case. Replacement therapy requires large amounts of injected proteins. As Elman and his group[102] have shown dietary nitrogen loss or gain in dogs is distributed between the tissue and serum proteins in a ratio of about 30:1. The protein stores of the tissues must be replenished as the value for plasma albumin is restored to normal. Clinical experience has shown that this may take considerable time.

Wherever possible, the administration of protein-building material rather than simple replacement therapy should be undertaken. The patient should be put on a high-protein diet, with adequate calories in carbohydrate and fat to spare protein catabolism.[103] Where the appetite is poor, intravenous alimentation with a protein digest or an adequate amino acid mixture may be used to supplement the oral protein intake. This type of therapy is just coming into its own,[104, 105] but there are still some practical difficulties in the intravenous injection of a sufficient amount of protein hydrolysate to maintain nitrogen balance. With surgical patients who cannot take any food by mouth, the addition of intravenous protein hydrolysates and parenteral vitamins to the conventional therapeutic regime of saline solution and glucose should do much to improve the postoperative course.[106] Unfortunately, there are some patients, particularly those with liver disease, in whom the synthetic processes are so impaired that replacement therapy with plasma may have to be given if the hypoalbuminemia is to be relieved. The enormous amounts required and the poor ultimate prognosis where liver function is seriously deranged make the value of such therapeutic efforts somewhat dubious. The favorable reports of Patek and Post[107] on improvement in some cases of cirrhosis of liver treated with a diet rich in proteins and the vitamin B complex suggest that definite return of the ability to synthesize albumin may occur on such a regime and that this is the procedure of choice in chronic liver disease. In acute hepatitis, the use of plasma to help tide a patient over a critical period of hypoalbuminemia may be indicated, since the ultimate outlook is fairly good.

It should be pointed out that the amounts of plasma protein required for the therapy of nephrotic hypoalbuminemia are large, since the deficiency of albumin is so extreme and the rate of loss in the urine so high. Until there is a better understanding of the fundamental disturbance in the nephrotic syndrome, however, some form of replacement therapy will have to be used in those patients whose edema does not respond to those simple measures or to those unknown factors that lead to diuresis in some patients. Binger and Goudsmit[108–110] have persistently advocated gum acacia in the treatment of nephrotic edema. There seems little doubt of its effectiveness in certain cases, and it has one great advantage over plasma protein — it is retained longer by the kidney and produces an increase in blood colloid. Unfortunately, acacia is deposited in the viscera, particularly the liver,

and may interfere with protein synthesis for that reason.[111] Hence, its use cannot be recommended. Concentrated human serum[112] and concentrated human albumin[113] have both been advocated. Use of the latter, particularly in aqueous solution, is rational, even though the amounts required are extremely large. Protein hydrolysates and amino acid mixtures provide means of increasing the supply of protein-forming material to nephrotic patients and have a role in the treatment of patients with good renal function, as Farr, Emerson and Futcher[114] have shown. In cases with poor renal function, the injected amino acids result in a rise of blood nonprotein nitrogen.[113]

Hypoglobulinemia

Deficiencies in certain globulins do occur and in certain cases can be rectified by appropriate therapy. The antibody globulins are frequently deficient, particularly in infants, since specific antibodies are probably not acquired except as a result of the stimulus of artificial immunization or from contact with the disease-producing agent. In many cases such contacts do not give rise to frank disease, but to latent infection or the carrier state, which may be equally effective in establishing immunity and stimulating antibody production.

Passive immunization is a form of replacement therapy whereby a specific antibody is supplied by injection of the serum from an immune person or an immunized animal. The use of heterologous antibody carries with it the risk of serum sickness, in which the lesions of periarteritis nodosa have recently been demonstrated.[115] Because the risk of serum disease is obviated, there is an increasing use of human serum for passive immunization, particularly in the prophylaxis of measles and pertussis and in the treatment of pertussis and scarlet fever.[116] The widespread use of whole-blood or plasma transfusions in infants with severe infections is based on the premise that the increased resistance of an adult is associated with an appreciable amount of circulating antibody that may be transferred to the infant. Although, as already pointed out, this is probably the case, studies analogous to those of Lyons on immuno-transfusion for hemolytic streptococcus infections are needed to put this practice on a more rational basis.[117]

Unfortunately, the fact that even human serum is not without its dangers has been forcibly brought home by the recognition of homologous serum jaundice. Recent studies indicate that this is probably due to a virus present in the blood of patients in the pre-jaundice stage of infectious hepatitis.[118] Fortunately, such cases had been comparatively rare in the United States, although cases have possibly gone unrecognized[119] until experience with yellow fever vaccine containing a small amount of icterogenic human serum brought this matter to the fore.[120] On the other hand, in England, where epidemic jaundice has been relatively common in recent years, many cases of the transfer of jaundice to patients by the injection of human serum, particularly convalescent measles and mumps serum, have been observed.[121] It is to be hoped that all clinicians using human blood, plasma and serum will keep careful records of the lot used, since this is essential for tracing the origin of the icterogenic agent when jaundice develops. The incubation period of this type of jaundice is from one to four months, so that unless a careful history is taken in all cases of jaundice the connection with an injection of human blood or its by-products may be overlooked. Studies on how to eliminate this danger are urgently needed.

The superiority of the method of therapy that depends on supplying the body with protein-forming materials is nowhere better illustrated than in the case of the antibodies. Here the protein-building material is easily supplied by the diet, but the stimulus to antibody formation must be provided by active immunization, which gives rise to a much more permanent and solid immunity than can be achieved by passive immunization. Cannon[122] has suggested that in severe protein deficiency the ability of the body to form antibodies may be impaired. The results of his further studies will be awaited with interest, since they may have an important bearing on the health of the malnourished populations of Europe in the coming period of reconstruction.

Complement deficiencies, as already pointed out, are rare, but deserve further study.[58] It is possible that the occasional salutary effect of blood or plasma transfusion in severe infections is due not only to the passive transfer of antibodies or to the supply of some of the needs of the body for protein but also to the passive transfer of preformed complement. Experimental studies in animals[123] have suggested the necessity of an adequate vitamin C level for complement activity, but subsequent experiments have failed to substantiate this in man.[124, 125]

Deficiency of clotting substances is frequently encountered in the clinic, usually owing to hypoprothrombinemia, but rarely, in cases of overwhelming liver damage, to fibrinogenopenia as well and, in cases of hemophilia, to lack of so-called "globulin substance." For the provision of these important globulins by replacement, fresh

or adequately preserved plasma must be used.[126] Either frozen or dried plasma is adequate, with preference for the frozen material, but commercial liquid plasma is inadequate, since it is kept under conditions that destroy the activity of these labile globulins and complement. Better than replacement therapy is the stimulation of prothrombin production by the administration of vitamin K. This is not usually successful where there is extensive liver damage. Unfortunately, no way of curing the coagulation defect of hemophilia other than blood or plasma transfusion is known, and the effect of such therapy lasts but a short time.

* * *

It is probable that the time may soon come when it will be possible to analyze protein deficiencies in terms of their individual components, and to supply the missing components in pure and highly concentrated form. It should, however, be emphasized that replacement therapy is a temporary measure, absolutely essential for acute emergencies, such as shock, acute infections and hemophilic crises. Equally important is the gathering of knowledge concerning the source and essential factors for the synthesis of the different functionally important plasma proteins. Again one is driven back to thinking about the functions of the tissues that are reflected in the pattern of the plasma proteins. In the case of prothrombin, the discovery that vitamin K is essential to its synthesis by the liver has made possible the rational treatment of prothrombin deficiency. Similar studies with regard to the other blood proteins — the essential dietary factors and amino acids necessary for their manufacture — should yield fundamental knowledge of great practical significance in clinical medicine and surgery.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 29461

PRESENTATION OF CASE

A thirty-eight-year-old librarian was admitted to the hospital because of chills, fever and weakness of two weeks' duration.

About seventeen years before entry the patient began to have intermittent attacks of diarrhea and melena that occurred at varying intervals of weeks to several months and lasted several days. During the attacks she was "rundown" and weak, while between the attacks she was quite normal jaundice. The attacks were not related to diarrhea and melena. Two weeks before entry she had a similar chill. She became progressively feverish, weak and tired, and developed generalized malaise. There was a sharp pain in the right lower anterior chest on eating or on deep inspiration. The pain did not radiate.

Physical examination showed a well-developed but thin, pale, feverish, dehydrated woman in no acute distress. The tongue, palate and pharynx were injected and coated with a white exudate. Chest expansion was limited by pain over the liver anteriorly. There were decreased breath sounds over the right base posteriorly. Transient rales were heard over both bases. The heart was of normal size, and the sounds were of good qual- and had normal bowel movements. Eleven years before admission she had an attack lasting for several weeks following which an ileostomy was performed. Her general condition improved and the ileostomy worked satisfactorily, requiring attention only about three times daily. Fecal discharge from the ileostomy was semisolid. Bowel movements from the rectum occurred about twice daily, except for brief bouts of increased frequency (five to ten a day) that occurred only about three or four times a year and lasted only one or two days. At these the stools were occasionally bloody but usually consisted of pink-staining mucus. She had an attack of chills and fever at intervals of several months. These lasted only a few hours and then subsided completely. There were associated malaise and occasional vomiting, but no ity and regular. A blowing apical systolic murmur was heard. The abdomen was soft and tympanitic, with "normal bowel sounds." Moderate tenderness was present over the left flank. The ileostomy appeared to be functioning well, but the surrounding tissue was red and macerated.

The blood pressure was 110 systolic, 58 diastolic. The temperature was 103°F., the pulse 120, and the respirations 28.

Examination of the blood showed a red-cell count of 2,760,000, with 6.2 gm. hemoglobin. The white-cell count was 45,900, with 95 per cent neutrophils. The blood chloride was 89.1 milliequiv. per liter. The nonprotein nitrogen was 24 mg. per 100 cc., and the protein 6.2 gm. One blood culture was negative. A second blood culture showed proteus bacilli that overgrew gram-positive cocci in pairs and diphtheroids. The urine had a specific gravity of 1.018 and showed a ++ test for albumin. The stools were guaiac negative.

Fluoroscopic examination of the chest showed that the motion of the right diaphragm was limited —about 0.5 cm.; the left moved normally. The right diaphragm was elevated. The liver was thought to be slightly larger than usual. There were several linear areas of atelectasis in the right lower lobe just above the diaphragm. There was also an area of increased density, measuring about 3 by 5 cm., apparently above the diaphragm. On the anteroposterior projection a shadow of decreased density was seen through the liver shadow, but this was not present in the lateral view. There was no fluid in the right base.

The patient was given daily intravenous infusions of 2000 cc. of 5 per cent glucose in physiologic saline solution and large doses of vitamins. On the second day she was given 5 gm. of sodium sulfadiazine, followed by daily doses of 2.5 gm. She received several transfusions. Her condition, however, became progressively worse. Despite a blood sulfadiazine level of 10 to 12 mg. per 100 cc., the temperature remained above 102°F. for the first two days, during which time she had two chills. For the next five days the temperature ranged between 100 and 105°F., with almost daily chills. The pulse varied between 90 and 150 for the first ten days. The patient became progressively weaker and slightly icteric. X-ray examination of the chest on the eighth day showed the previously described area of increased density in the right lower chest to have increased in size. The serum bilirubin was 3.0 mg. per 100 cc. direct and 3.4 mg. indirect. A repeat van den Bergh two days later revealed the serum bilirubin to be 3.8 mg. per 100 cc. direct, and 5.3 mg. indirect.

During the second week the patient had fewer chills. The temperature remained between 101

*On leave of absence.

and 103°F. The pulse gradually rose to 150. She became dyspneic and cyanotic, and a gallop rhythm developed. The respirations became more difficult. The patient became comatose and died on the fifteenth hospital day.

Differential Diagnosis

Dr. Wyman Richardson: I see no reason to doubt the fact that this patient had chronic ulcerative colitis for which she was given an ileostomy, apparently with considerable improvement. In spite of the fact that she had this illness before the Chicago Fair, it is possible for one to have amebic disease even though one does not go to fairs. I shall bring that point up again in a moment.

Beginning with the premise that she had chronic idiopathic ulcerative colitis and that this had gone on to bring about her death, I should like to start the discussion with the total white-cell count, which was very high — 46,000. One thinks of causes that will produce as high a white-cell count as that and they are not too numerous, especially in an adult. They are, in general, infection, infarction and tumor. We probably can rule out leukemia of the obvious type on the basis of the blood picture, but if we take these three things, infection, infarction and tumor, and consider them from the point of view of this case, we can get some help from this white-cell count. In infection there is, as you know, a polymorphonuclear leukocytosis that is almost 100 per cent in severe infections. In this case there is said to have been 95 per cent neutrophils; the other 5 per cent are not quoted but were undoubtedly lymphocytes. If there were monocytes, my argument would not hold water very well. Massive infarction, on the other hand, will also produce a very high white-cell count. As you know, patients with mesenteric thrombosis may have a total white-cell count higher than this. In these cases of massive infarction, however, the leukocytosis is much more nearly a total leukocytosis, with increase not only in the polymorphonuclear cells but also in the lymphocytes and monocytes, so that the differential picture is much more nearly like that seen in normal blood. This is not just talk because it has been possible to differentiate infarction and infection by examination of the smear alone. This count therefore tends to militate against massive infarction. Tumor, particularly bronchiogenic carcinoma or carcinoma of the liver, may also produce leukocytosis or a leukemoid blood picture, but in these cases, more often than not, one finds a blood picture showing marked evidence of red-cell regeneration, presumably when the marrow is involved, and one is not so likely to see the complete polymorphonuclear leukocytosis that one does in infection. Also, there are qualitative changes in the cells, which I shall not discuss because we have not the smear before us, and also because I have recently emphasized this too much in discussing other cases. So the evidence from this finding alone is that this patient had infection, rather massive infection with large areas of tissue destruction because of the very high white-cell count. I might add if there is not a considerable area of tissue destruction, and if there is not either a large abscess or many small ones, one does not obtain a great increase in the white-cell count. In a septicemia without abscess formation, even acute septicemia or acute endocarditis, the white-cell count is often at a normal or less than normal level.

I believe that the blood chloride was low because of the diarrhea and sweating.

I shall comment briefly about the bilirubin. The patient was definitely icteric, and the direct reaction of the van den Bergh test was in great preponderance over the indirect, that is, the total percentage of direct bilirubin was about 85. This suggests obstructive jaundice.

If one takes this picture and forgets the x-ray examination for the moment, it seems to me that we have a patient with ulcerative disease of the bowel, and that she very likely developed — as so frequently happens — a thrombophlebitis or pylephlebitis, which could have involved the system of veins that go to the liver, with the subsequent development of either a single abscess or probably multiple abscesses of the liver. One should consider the possibility of subdiaphragmatic abscess. That still is a possibility, but it would not account for the jaundice. If one explains the jaundice on the basis of liver abscess it seems to me that there is evidence in favor of multiple abscesses, possibly associated also with a low-grade infection of the small ducts, a cholangitis. This is rather definite evidence against subdiaphragmatic abscess. One other bit of evidence is the lack of fluid above the diaphragm, which so often occurs in subdiaphragmatic abscess. There are no data from this record that enable me to rule out amebic abscess, but I believe that it was adequately ruled out. One would ordinarily have to keep that in mind.

I have reached the point where I shall call this liver abscess, probably multiple, with perhaps at least one large one. I should like to stop there, but unfortunately there is a 3-by-5-cm. mass in the chest that does not seem to be readily explained.

Dr. Milford Schulz: I do not see the mass on this film. All I can see can be explained by an elevated diaphragm and atelectasis.

DR. CHESTER M. JONES: That is what the doctor who took care of him thought.

DR. SCHULZ: There is no fluid in the chest that I can see. The liver is enlarged.

DR. RICHARDSON: What about the area of decreased density?

DR. SCHULZ: I cannot see that either. This is a gas bubble in the stomach. Someone may have requested films with greater penetration, which showed an area of decreased density in the liver; but it does not show in this film. Everything here indicates atelectasis and an elevated diaphragm, probably due to faulty respiratory effort.

DR. RICHARDSON: Usually when I come to this last stretch I know which horse I am going to bet on. Today I was going to make up my mind after seeing the x-ray films. I was thinking of two things. One was pulmonary infarct, but there was no history of cough with sputum and I was reluctant to accept that. The other possibility was coincidental carcinoma of the lung. From the appearance of the film and from Dr. Schulz's discussion I think that I shall leave the diagnosis as I originally stated it; I shall disregard this area of increased density and say that it was due to atelectasis. My diagnosis is chronic idiopathic ulcerative colitis with liver abscess.

DR. JONES: I am sorry that Dr. McKittrick is not here. This patient was very interesting. Dr. McKittrick and I felt that she had intrahepatic sepsis. As she was followed through her illness there was more and more compression tenderness over the liver, and some right subcostal tenderness. As a rule these signs when combined with a septic temperature are diagnostic of infection within the liver. The liver itself could be palpated even without compression and was quite tender. Before her death we were certain that she had abscess formation in the liver. Because of the succession of chills and fever I thought, and I believe Dr. McKittrick felt the same way, that there were multiple abscesses rather than a single one. Dr. Richardson mentioned the remote possibility of amebic abscess. As a rule a leukocytosis of this degree does not occur with amebic abscess; usually there is only a moderate leukocytosis. The fever can be extremely high in either amebic abscess or amebic hepatitis, but one usually does not get the combination of chills and fever and the intense leukocytosis that was present here.

There are one or two points I should like to add. In the first place there was no excuse for her developing such serious complications in her illness. This should represent a criticism of the medical treatment. The reason was that after ileostomy she was reluctant to see a physician for any symptoms whatever and subsequently kept away from all physicians. Another point that is worth mentioning is the paucity of cases of ulcerative colitis that show intrahepatic disease. I have always thought that, with serious infection in the bowel draining eventually into the portal area, hepatic disease should develop more frequently. We have, however, seen only two or three cases associated with ulcerative colitis. It is the exception rather than the rule. When infection does occur it is usually localized in the pelvis or perianal region.

I was under the impression that there was one film that did show a probable cavity in the liver substance. On the basis of that and of the clinical picture, roentgenograms were taken after the administration of thoratrast to determine whether there was a single abscess or multiple ones.

DR. SCHULZ: We have the films here. The liver is riddled with multiple abscesses, which are in contrast to the liver substance where the thoratrast was taken up by the Kupffer cells.

CLINICAL DIAGNOSES

Multiple liver abscesses.
Ulcerative colitis.

DR. RICHARDSON'S DIAGNOSES

Chronic idiopathic ulcerative colitis.
Multiple liver abscesses.

ANATOMICAL DIAGNOSES

Ulcerative colitis, chronic.
Pylephlebitis, with liver abscesses, multiple.
Pulmonary atelectasis.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The autopsy on this patient showed evidence of long-standing, ulcerative colitis with little if any activity. The bowel wall was markedly thickened, so-called "hose-like," with a very narrow lumen. The widest circumference of the bowel was 2.5 cm., about a quarter of the normal bowel circumference, and at one point it was 1.5 cm. with only a tiny lumen. This atrophy was obviously due to disuse. (In one case, which came to autopsy about ten years after ileostomy, the rectum and sigmoid were so atrophic that in places no lumen could be found.) The liver was adherent to the diaphragm on the right side, was extremely large, weighing 3500 gm., and contained multiple abscesses (Fig. 1). The main portal vein contained an infected thrombus, which extended into both radicles, more into the right than into the left. There was also free pus in the

portal veins. There were many large, greenish abscesses throughout the liver. It is quite obvious that surgical drainage of so many abscesses would have been impossible. We cultured the abscesses and the blood, but recovered only proteus bacilli. The spleen weighed 450 gm., and there was thrombosis in the splenic vein. Although we examined many of the veins in the pericolic fat we were not able to find the actual source of the liver abscesses. Nevertheless, the hepatic infection was unquestionably secondary to the colitis.

FIGURE 1. *Photograph of Cross Section of Liver Showing Multiple Abscesses and Portal-Vein Thrombosis.*

The bone marrow showed a marked myeloid hyperplasia with replacement of the fat cells. We found nothing but atelectasis in the lung to account for the roentgen shadows in the right lower lobe. This is the only case of liver abscess associated with idiopathic ulcerative colitis that I can recall.

CASE 29462

PRESENTATION OF CASE

An eighteen-year-old boy was first seen in the Out Patient Department, about one year before the present admission, because of hemoptysis of four years' duration.

At the age of thirteen, while playing, he coughed up several large blood clots. He had a similar episode one week later, and these were repeated intermittently up to the day of his visit to the Out Patient Department. The amounts raised varied from a speck to half a cupful. No definite statement was made concerning the frequency of attacks, but "at no time were they more than two weeks apart." There were no chills, fever, night sweats or chest pain until "recently," when he had noted sharp twinges of pain in the right upper chest unassociated with cough or hemoptysis. There had been no history of inhalation of foreign body, antecedent upper respiratory infection, known contact with tuberculosis or undue bleeding tendency. He had fractured the left collar bone one year before onset of his symptoms, for which he was in a cast for two months.

Examination in the Out Patient Department showed a well-developed and well-nourished boy in no distress. The chest was well developed. There was dullness over the right upper lobe posteriorly to the midscapular region and anteriorly to the fourth rib, with occasional expiratory bubbling and coarse crepitant rales posteriorly. Krönig's isthmus was slightly narrowed on the right. The lungs were otherwise clear. The heart was in its usual position and normal in size. The abdomen was negative. There was no clubbing of the fingers.

The blood pressure was 138 systolic, 68 diastolic. The temperature was 98°F., the pulse 60, and the respirations 20.

X-ray examination of the chest showed a round, homogeneous soft-tissue mass in the upper posterior mediastinum measuring approximately 11.5 cm. in diameter, without any evidence of calcification or cavity formation. The tumor obliterated the upper portion of the right lung but the visible portion of the right lung and the left lung

appeared clear. The hilar shadows were normal and equal on both sides. The heart was not remarkable. No definite bone involvement could be seen, but there was a questionable pressure defect on the right lateral aspect of the fourth dorsal vertebra, with narrowing of the right pedicle. The trachea appeared straight in the midline, and there was no mediastinal displacement. No fluid was present. Bucky films of the chest confirmed the presence of the large mass in the lung. An area of probable slight erosion of the upper aspect of the sixth rib was also seen. There was an irregular air pattern in the region of the mass, probably due to partially collapsed lung that was superimposed on the shadow of the mass (Fig. 1).

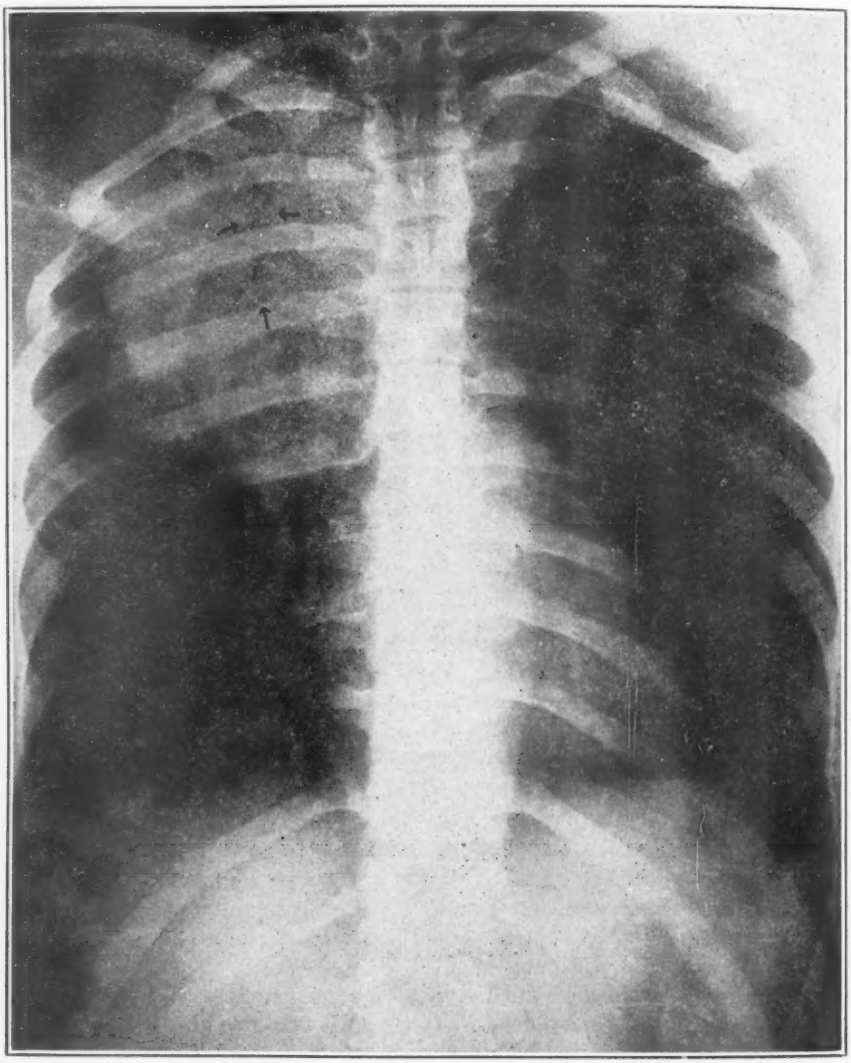

FIGURE 1. *Chest Roentgenogram (Bucky) Showing Mass in the Right Upper Chest. The arrows point to the irregular area discussed in text.*

While being followed in the Out Patient Department, the patient developed wheezing, especially at night. No other information was given regarding these attacks except that "he was quite free of wheezes at times." He was free of pain and maintained his weight. Bronchoscopy showed "extrinsic pressure but failed to reveal the source of the bleeding, although a moderate amount of bright-red blood was seen in the trachea and right main bronchus." Hospitalization was advised but refused.

For the next ten months he remained free from pain, hemoptysis and cough. At the end of this period he obtained a job in a weaving mill, doing heavy labor. Eight days before entry he suddenly became dyspneic while working. The dyspnea forced him to leave his work. Six days prior to admission he developed severe pain in the right anterior chest and he was admitted to a commu-

nity hospital, where x-ray films showed a lobulated tumor mass in the upper half of the right lung, with pleural effusion. Two chest taps yielded 100 and 300 cc. of reddish-brown pleural fluid and gave considerable relief. He was transferred to this hospital.

Physical examination showed a poorly nourished, cyanotic and dyspneic man with anxious, pale facies and visible flaring of the alae nasi on breathing. The right chest was splinted during inspiration. There were dullness and diminished tactile fremitus and breath sounds over the right upper and lower lobes. Dullness was obtained over the right middle lobe, with egophony and increased tactile fremitus. Pectoriloquy was heard over the right upper lobe posteriorly and over the middle lobe anteriorly. The diaphragmatic excursion was poor on the right. The heart was normal. The remainder of the examination was not remarkable.

The blood pressure was 130 systolic, 60 diastolic. The temperature was 99.6°F., the pulse 128, and the respirations 25.

Examination of the blood showed a red-cell count of 4,100,000, with 75 per cent hemoglobin. The white-cell count was 11,000 with 89 per cent neutrophils. A blood Hinton test was negative. The prothrombin time was 28 seconds (normal, 16 seconds); the hematocrit was 39.2 per cent. The nonprotein nitrogen was 10 mg. per 100 cc., and the protein 5 gm. The van den Bergh test was normal. Urinalysis was negative.

X-ray examination of the chest, almost a year after the first one, showed the tumor mass still present. The right pleural cavity was filled with a fairly large amount of fluid and there was partial collapse of the right middle and lower lobes, which had a honeycombed appearance. The left lung appeared clear, but there was questionable crowding of the markings in the left lower lobe.

During the next ten days, three chest taps yielded 2800, 1500 and 1000 cc. of dark, bloody fluid, which on smear and culture was negative for organisms. No tumor cells were seen in the sediment.

Repeated x-ray studies after the taps showed that, instead of a fluid level, there was an area of increased density with irregular markings extending along the lateral axillary line. There were numerous irregular areas of decreased density in the right upper chest, either in the tumor or in the pleural cavity. None of the visualized bones, especially the ribs, showed evidence of destruction, and no other changes were noted. Another bronchoscopy, a year after the first, was negative. No evidence of intrinsic or extrinsic tumor was seen.

On the eleventh hospital day an operation was performed.

Differential Diagnosis

Dr. Austin Brues: I should like to discuss this case mainly from the standpoint of its natural history, which seems rather specific and characteristic. The boy had a lesion that had apparently existed for at least five years and first gave symptoms at the age of thirteen. The history divides itself into three phases. First, there was a long period in which the only symptom was rather persistent hemoptysis. Secondly, after four or more years there was a period of wheezing, suggesting bronchial compression. Finally, there was an acute sudden episode with pain in the anterior chest and dyspnea, and the rapid development of bloody pleural effusion. To this history we can add the finding of a round mass inside the chest, apparently arising from the posterior mediastinum, and presumably the seat of the symptoms. We have no evidence of disease elsewhere in the body, except that he had a prolonged prothrombin time and a low serum protein. However, the van den Bergh test was normal, and we have insufficient evidence to implicate the liver.

The question that we have to settle is, What sort of isolated mass in this location will progress to give this sort of history? Obviously this was not an acute infectious process. It might conceivably have been due to tuberculosis of the bronchial nodes or to tuberculosis arising from the spine. The entire early course of the process, however, was essentially silent except for hemoptysis, and there was no evidence of infection or tuberculosis elsewhere. I consider that an infectious process of any sort is unlikely. A hydatid cyst of the mediastinum, first giving rupture into the bronchus, later into the pleural cavity, might give rise to this sequence of symptoms; but we have no reason to suspect an unusual environmental association and the patient had no eosinophilia. Moreover, no eosinophilia was noted even after extension of the process into the pleural cavity, which, if due to rupture of a hydatid cyst, would have caused a certain amount of the cyst contents to be absorbed.

In a young patient we must think of a congenital anomaly — bronchostenosis or a lung cyst. A condition of this sort would most likely progress to serious symptoms only if it became secondarily infected. Again I point out that infection was not a perceptible element in the clinical picture.

This brings me to tumor. The long duration is in favor of a benign tumor or a tumor that underwent malignant change late, that is, during the last year. Lymphoma can exist for a period of

many years without characteristic progression. Such a lymphoma would be the giant follicular type or a very scirrhous type of Hodgkin's disease. I should point out that hemoptysis is a rare symptom in lymphoma, and if it does occur it suggests that one is dealing with a particularly invasive form, which would not be the type giving a long, relatively quiescent history. It seems to me the presumptive diagnosis is a teratoma, not well enough differentiated, as is the classic dermoid cyst, to show calcification by x-ray or to yield hairs or other recognizable elements in the sputum or pleural fluid. The life history of this process is emphatically in favor of this diagnosis. These tumors appear early in life, may give their first symptoms at puberty or later, and sometimes give hemoptysis over a long period. Eventually they are likely to undergo malignant change or to rupture. I should be in favor of rupture as the explanation of the final episode here because of the extreme acuteness of its onset, although invasion of the pleura is a possible explanation, and would point to malignant change. I do not believe that it is necessary to assume, however, that the process had become malignant.

The fly in the ointment is the location of the lesion. It was apparently posterior in position, whereas dermoid cysts and teratoid tumors are almost always found in the anterior mediastinum.

Typical neoplasms of the posterior mediastinum are of neural origin. The history, however, is against one of these. They grow behind the pleura, and one would not expect cough and hemoptysis to be the earliest symptoms. Because of their location they frequently produce Horner's syndrome or pain early in the course of their development. The first symptom here was hemoptysis, which suggests that the lesion was near the bronchi and not posterior to the pleura. There are various rare tumors, such as chondroma, endothelioma, angioma and lipoma, that might arise in this location. There is one thing somewhat in favor of the possibility of an angiomatous tumor — the characteristic picture of bleeding with which the history started.

I wonder if we might see the x-ray films.

Dr. Laurence L. Robbins: These films show a fairly smooth mass arising posteriorly in the mediastinum, or apparently arising in the mediastinum. The one thing in favor of the neural type of tumor, in addition to its location posteriorly, is that there is a definite erosion of the pedicle of the fourth thoracic vertebra. So far as the ribs are concerned, I am not at all sure that there are any definite changes. This is the shadow described as an irregular area overlying the mass and representing aerated lung (Fig. 1). I am not convinced of that. The only other possibility is that it is fat within the tumor. It is difficult to be sure, and most likely it is air in the overlying lung.

These are the films taken at the time of the second admission; they show a large amount of fluid in the pleural cavity and disease in the right lower lobe. The mass and the shadow, which is either air or fat, are still present. This view, with the patient on his side, was taken after a tap to determine whether there were pleural metastases. There are irregularities along the pleura, but they are most likely masses of fibrin rather than metastases, because fibrin is usually present with bloody fluid. One cannot, however, positively rule out metastases.

Dr. Brues: I am going to let my diagnosis rest on the history rather than on the location and to assume that the tumor arose near the bronchi rather than posterior to the pleura. I shall say that it was a teratoid tumor.

Dr. Richard H. Sweet: Might I say as a representative of the service that saw the man before he was operated on that we did not believe, at least I did not believe, that he had a benign tumor. In fact I have never seen a benign mediastinal tumor produce bloody effusion. My personal diagnosis was, and I suspect some of the others who saw the patient were of the same opinion, a malignant tumor, probably teratoma. Dr. Brown operated on this patient. What does he say?

Dr. Robert K. Brown: We did a thoracoscopy and did not see much except a large empty space with implants of fibrin on the chest wall. Biopsies were taken of these and they were not malignant. Since we still thought that the tumor was malignant, the patient was explored. The preoperative diagnosis was malignant neurogenic tumor or neurofibrosarcoma, because we thought that it arose in the posterior mediastinum.

At operation there was a large cystic mass in the upper part of the right thorax. This contained a hole, and the rupture was probably the cause of the bloody pleural fluid. A biopsy specimen was taken from the wall of the cystic mass at the edge of the rupture, and on cutting, it was evident that there was lung tissue adherent to the wall of the mass. I thought this was collapsed lung plastered over the cyst. The patient died following operation.

Dr. Benjamin Castleman: Would anyone want to venture a diagnosis at this point?

Dr. Ralph Adams: I have no idea what was wrong with this man. I think that the lesion arose in his lung because of two factors that almost have to place it in the lung. First, there was frequently recurring hemoptysis. There was

a rule here a few years ago that daily hemoptysis meant carcinoma. After three years we found an exception in a case of bronchiectasis. That was the first exception, and I have since encountered one other. In the second place, this man had a wheeze, indicative of developing bronchial obstruction. My personal diagnosis, if I were about to operate, would be slowly growing sarcoma of the lung. I believe that sarcoma in the lung has occurred in this hospital only once.

DR. SWEET: That is correct.

DR. ROBBINS: How do you explain the erosion of the pedicle of the fourth thoracic vertebra if it is a primary lung tumor?

DR. ADAMS: I could not explain it as a primary lung tumor unless it were sarcoma of the lung. If it were a sarcoma arising in the mediastinum and invading the lung the explanation would be easy.

DR. GEORGE W. HOLMES: Is there anything to show why there was such a delay between the first roentgenologic examination and operation?

DR. CASTLEMAN: The patient refused operation.

CLINICAL DIAGNOSIS

Superior mediastinal tumor, with rupture into the pleural cavity.

DR. BRUES'S DIAGNOSIS

Teratoid tumor of mediastinum, with rupture into the pleural cavity.

ANATOMICAL DIAGNOSIS

Neurofibroma of lung, with cystic degeneration and rupture into the pleural cavity.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The material that Dr. Brown removed from the cyst or tumor was composed of spindle-shaped cells, some in whorls, which strongly suggested a neurogenic benign tumor. In favor of this was the presence of huge numbers of so-called "foam cells," that is, large lipoid-laden mononuclear cells. That is probably the reason why Dr. Robbins thought he saw fat in the tumor. Certainly a large part of the tumor was composed of cells filled with fat. Lipoid degeneration of a neurofibroma is not at all uncommon. We were fairly certain that the tumor was benign.

The autopsy specimen shows that this tumor was within the lung. It had broken down so much that it had become cystic. This cystic mass, which was about 7 or 8 cm. in diameter, communicated with the apical branch of the right upper lobe bronchus, and this certainly accounted for the long-standing hemoptysis. I believe that the tumor probably arose close to the bronchus, or perhaps in it, and degenerated slowly as it gradually increased in size. There was lung tissue surrounding the cyst on all sides except over the area where it had ruptured.

We have had 2 other cases of neurofibroma of the lung. One was in a man of thirty who had all the signs and symptoms of a bronchial adenoma, that is, bronchial obstruction with hemoptysis. Bronchoscopic biopsy showed it to be a neurofibroma, and Dr. Benedict removed the tumor via the bronchoscope in three operations.

DR. EDWARD B. BENEDICT: The patient was completely relieved by bronchoscopy. I have not seen him for three years. He had no apparent lung damage.

DR. CASTLEMAN: The other case was one in which Dr. Churchill performed a lobectomy for a well-circumscribed tumor that pressed on a bronchus but had not actually invaded its mucosa.

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THE JOURNAL does not hold itself responsible for statements made by any contributor.

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UNITED WAR FUND

No one knows better than physicians the valuable contribution to community life made by the two hundred and sixty-four hospitals, dispensaries, clinics and other health and social services that share in the Greater Boston Community Fund. Possibly no group of citizens gives more of itself to the 400,000 persons who depend on these agencies to help adjust themselves to life's problems. In either case, or perhaps because of both, physicians of Greater Boston are bound to be generous to the appeal now being made for these community services. But that's not all. The $7,500,000 goes two ways. Whereas approximately $5,500,000 is allocated to Community Fund needs, $2,000,000 goes directly to such war-related services as the USO, War Prisoners Aid, United Seamen's Service and relief of the stricken peoples of the Allies.

The physician must think twice when the solicitor asks for his gift this year. He will want, first of all, to do something for that bright-eyed little youngster whose parents have deserted him. Then, of course, he must help the USO, which is doing such a magnificent job everywhere, and he cannot resist the appeal to make a token gift for all the brave people overseas who are suffering unknown hardships in this war, while he and his family live safely and snugly at home. GIVE — BECAUSE YOU CARE.

SO LITTLE TIME

THE majority of us are so constantly confronted with the perplexing problem of fitting our commitments into an allotted daily twenty-four hours that we view with amazement and despair the activities of individuals like, let us say, Prime Minister Churchill. Writer of history and maker of history, he has found time in his abundant life to fight in one war and direct another, to make books and speeches, to lay bricks, to paint pictures and to save an empire.

John Buchan, later Lord Tweedsmuir, was a writer of note before he became a statesman and finally governor general of Canada; we are familiar with the dual activities of Disraeli, romantic novelist and statesman without peer, who presented Queen Victoria with the empire that Churchill has kept intact; Bulwer-Lytton was a novelist and statesman, if not pre-eminent as either; General Lew Wallace wrote one of our really outstanding historical novels; and General Patton, we are told, is a poet of no little merit! These men, whether satisfied with their achievements or not, have at least found time to make some contributions to the world in which they found themselves.

It is a common experience of those who are sensitive to life, who feel the need of some personal

fulfillment, some satisfying justification for their existence, to awaken rather late, and suddenly, to a realization of life's self limitation. The allotted years are never really enough, nor does anyone know the sum and extent of his allotment. We accumulate, as we go, a squirrel cage full of little duties and activities that may keep us moderately comfortable because of a real communion with ourselves, but we seldom find time to realize the dreams of youth or to search out the various talents that may lie in each one of us. We use our work and our play, our recreations and our amusements, as anodynes to keep us from a full realization of our relative futility.

Some stern moral censor devised a comfortless motto for sundials. What could possibly be more effective than the ominous epigram, "It is later than you think," to destroy the pleasure of a sunny hour in a garden? John Marquand must have been deciphering this legend just before he developed the theme of middle-aged frustration in his newest book, *So Little Time*. Middle age is a bit late to realize how little time there is, but it is the period of life at which we usually appreciate it — except, perhaps, for those happy extroverts who never realize it at all.

Time is an elusive commodity, and the greatest gift that man can have or develop is the ability to use it intelligently, if not industriously. Every individual is given the same amount of time in each twenty-four hours — which sounds like a truism, but is really a fundamental and dimly appreciated truth. The only difference in this respect is that some of us are given more units to use than are others. Next in importance is a sense of values that will help us to see clearly those of our own qualities that can be developed and the wishes that can reasonably be fulfilled. If we wish to avoid frustrations, we must choose the goal that is within our reach, we must work steadily toward it, and we must start early enough. The only qualification that need apply to this goal is that it must satisfy the person who is seeking it.

MEDICAL EPONYM

Kümmell's Disease

Professor Hermann Kümmell (1852–1937) described this condition in a paper, entitled "Die rareficirende Ostitis der Wirbelkörper [Rarefactive Ostitis of the Vertebral Bodies]," published in the *Verhandlungen der Gesellschaft deutscher Naturforscher und Aertze* (**64:** 282–285, 1892). A portion of the translation follows:

> . . . . To sum up, we are dealing with an injury, often of trifling nature, that affects the vertebral column either directly or indirectly, and so far as the immediate effect is concerned, leaves no sign of its occurrence. After months of complete health, there begins a rarefactive process in the vertebras, which finally results in atrophy of their substance. Suppuration does not occur in this pathologic process, as in tuberculous spondylitis, nor is there any thickening of the bony mass, as in syphilitic processes, or bony deposition and change, as in arthritis deformans. . . .
>
> The diagnosis of the condition, after what has been said, offers no great difficulties; and if we consider the most important factors — the effect of trauma in an otherwise healthy person, transitory pains and gibbus formation later, with the accompanying local and referred discomfort — confusion with tuberculous spondylitis or other disease of the vertebras is easily avoided.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

CUSHMAN — Howard L. Cushman, M.D., of Methuen, died November 4. He was in his fifty-eighth year.

Dr. Cushman received his degree from Boston University School of Medicine in 1908. Up to the time of his death, he served as school physician in Methuen. He was a member of the Massachusetts Medical Society, the American Medical Association, the Lawrence Medical Association and the Lawrence Medical Club.

His widow and a brother survive.

DAVID — Ernest J. David, M.D., of Lowell, died July 11. He was in his sixtieth year.

Dr. David received his degree from Laval University Faculty of Medicine, Quebec, in 1915. He was a member of the Massachusetts Medical Society and the American Medical Association.

HALLORAN — Roy D. Halloran, M.D., of Waltham, died November 10. He was in his fiftieth year.

Dr. Halloran received his degree from Columbia University College of Physicians and Surgeons, New York, in 1920. He served as an intern at the Newark (New Jersey) City Hospital from 1920 to 1922 and later as assistant physician at the New Hampshire State Hospital in Concord. He joined the staff of the Boston State Hospital in 1922 and served as assistant superintendent in 1928 and 1929. In 1925 he and Dr. Abraham Myerson, of Boston, founded the hospital's research department. In

1933 Dr. Halloran was named the first superintendent of the Metropolitan State Hospital, a post that he held until he took leave of absence in July, 1942, to be commissioned a colonel in the Army Medical Corps. His job in the Army was to organize and co-ordinate the neuropsychiatric service in all Army branches, at home and overseas. He was a member of the American Psychiatric Association, New England Society of Psychiatry, Massachusetts Medical Society and American Medical Association, as well as professor of clinical psychiatry at Tufts College Medical School.

His widow, a daughter and a son survive.

KENNISON — FREDERICK M. KENNISON, M.D., of Boston, died July 31. He was in his eighty-first year.

Dr. Kennison received his degree from Tufts College Medical School in 1905. He was a member of the Massachusetts Medical Society and the American Medical Association.

MILLER — HOWARD S. MILLER, M.D., of Taunton, died September 6. He was in his fifty-sixth year.

Dr. Miller received his degree from Middlesex University School of Medicine, Waltham, in 1922. He was a member of the Massachusetts Medical Society and the American Medical Association.

THOMPSON — CLARA L. THOMPSON, M.D., of Boston, died September 16. She was in her seventy-third year.

Dr. Thompson received her degree from the College of Physicians and Surgeons, Boston, in 1915. She was a member of the Massachusetts Medical Society and the American Medical Association.

WASHBURN — FRANK H. WASHBURN, M.D., of Holden, died November 10. He was in his seventy-third year.

Dr. Washburn received his degree from Tufts College Medical School in 1899. Dean of physicians in Holden, he was a founder and chief surgeon at the district hospital and a fellow of the American College of Surgeons. He was consulting surgeon at the state sanatorium and the United States Veterans Hospital, both in Rutland Heights. He was a councilor of the Massachusetts Medical Society, past president of the Worcester District Medical Society, a member of the American Medical Association, American Urological Association, New England Urological Society, Trudeau Society, American Society of Regional Anaesthesia and the New England Roentgen Ray Society.

His widow, a daughter and two sons survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

GONOCOCCUS CULTURE SERVICE

The Massachusetts Department of Public Health announces a new service to physicians of Massachusetts. The superiority of cultural methods over smear methods in detecting gonococci in certain types of gonococcal infections is now well recognized, and the department is of the opinion that utilization of cultural methods will be of aid in the control of such infections.

Mailing of specimens. Recent advances in methods of sending specimens through the mail for cultural studies indicate that such delayed cultures are less efficient than cultures planted immediately after obtaining the specimens, but considerably more efficient than the examination of stained smears. Any physician wishing to utilize this service should request mailing kits from the Bacteriological Laboratory, Room 527, State House, Boston. Instructions for obtaining specimens will accompany each mailing outfit.

Storage of mailing outfits. The fluid in which the specimens are placed for mailing will maintain its efficiency only if kept in the icebox, and for a period not to exceed six weeks. All containers will be stamped with an expiration date, and if not used by that time they should be returned to the laboratory, whereupon fresh outfits will be sent to the physician on request. It should be emphasized that mailing outfits kept at room temperature before being inoculated do not give satisfactory results.

Relative value of cultures. Cultures are but slightly more efficient than smears in detecting gonococci in male patients who have a purulent urethral discharge, but far more efficient than smears in detecting gonococci in prostatic secretions as a test of cure. Cultures are more efficient than smears in detecting gonococci in both adult and immature females in all stages of gonococcal infection.

Precautions to ensure satisfactory specimens. The efficiency of the cultural method depends greatly on the physician's care and expertness in obtaining satisfactory specimens. The instructions on the card in the outfit are brief but if followed in detail should ensure satisfactory specimens.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR OCTOBER, 1943

RÉSUMÉ

DISEASES	OCTOBER 1943	OCTOBER 1942	SEVEN-YEAR MEDIAN
Anterior poliomyelitis	57	5	11
Chicken pox	485	291	333
Diphtheria	18	11	15
Dog bite	721	812	812
Dysentery, bacillary	24	314	21
German measles	82	57	35
Gonorrhea	435	384	416
Measles	402	541	291
Meningitis, meningococcal	45	11	6
Meningitis, other forms	13	3	*
Meningitis, undetermined	11	0	*
Mumps	158	401	204
Pneumonia, lobar	161	242	227
Salmonella infections	14	13	3
Scarlet fever	624	621	362
Syphilis	380	610	450
Tuberculosis, pulmonary	259	236	238
Tuberculosis, other forms	16	11	29
Typhoid fever	4	7	7
Undulant fever	6	6	5
Whooping cough	322	731	555

*Pfeiffer-bacillus meningitis only other form reportable previous to 1941.

COMMENTS

The month of October has produced a long list of diseases more or less above the seven-year median. Anterior poliomyelitis is still at a point five times that of the seven-year median, but, on the other hand, the current

month's figure is less than half that of last month. Apparently the summer's outbreak is well on the wane.

Scarlet fever, which has been at an unusually high level all this year, seems to have begun again the usual seasonal upswing following the summer drop.

Geographical Distribution of Certain Diseases

Anterior poliomyelitis was reported from: Amherst, 1; Arlington, 1; Attleboro, 3; Beverly, 7; Boston, 2; Cambridge, 2; Danvers, 3; Fall River, 6; Fitchburg, 1; Hamilton, 1; Hopedale, 1; Ipswich, 1; Lee, 1; Lowell, 2; Lynn, 2; Medford, 2; Methuen, 1; Natick, 3; New Bedford, 2; North Attleboro, 1; North Reading, 1; Norwood, 1; Plymouth, 1; Quincy, 1; Saugus, 1; Seekonk, 1; Swansea, 2; Topsfield, 1; Waltham, 2; Walpole, 1; Watertown, 1; Weymouth, 1; total, 57.

Anthrax was reported from: Haverhill, 1; total, 1.

Diphtheria was reported from: Boston, 6; Bourne, 1; Chicopee, 1; Lowell, 3; Medford, 1; New Bedford, 2; Salem, 2; Somerville, 1; Taunton, 1; total, 18.

Dysentery, bacillary, was reported from: Beverly, 2; Boston, 3; Brockton, 1; Brookfield, 1; Cambridge, 1; Easthampton, 1; Malden, 11; Northampton, 1; Wellesley, 3; total, 24.

Encephalitis, infectious, was reported from: Worcester, 1; total, 1.

Malaria was reported from: Amherst, 2; Brookline, 1; Fort Banks, 11; Fort Devens, 2; total, 16.

Meningitis, meningococcal, was reported from: Arlington, 1; Beverly, 1; Boston, 12; Brookline, 1; Cambridge, 1; Chelsea, 2; Chelsea Naval Hospital, 3; Fall River, 1; Fort Devens, 2; Framingham, 1; Lowell, 1; Needham, 1; New Bedford, 1; Newburyport, 1; Newton, 1; North Brookfield, 1; Plymouth, 1; Salem, 1; Scituate, 1; Somerville, 1; Southbridge, 1; Waltham, 2; Wellesley, 1; Weymouth, 1; Winthrop, 1; Worcester, 4; total, 45.

Meningitis, other forms, was reported from: Boston, 3; Cambridge, 1; Haverhill, 1; Ipswich, 1; Marblehead, 1; Medford, 1; Methuen, 1; Northbridge, 1; Salem, 1; Springfield, 1; Waltham, 1; total, 13.

Meningitis, undetermined, was reported from: Boston, 4; Milton, 1; Palmer, 1; Quincy, 2; Springfield, 1; Worcester, 2; total, 11.

Salmonella infections were reported from: Boston, 1; Bridgewater, 1; Cambridge, 1; Chelsea, 1; Chicopee, 2; Leominster, 1; Lowell, 1; Lynn, 2; Medford, 1; Westboro, 1; Weymouth, 1; Worcester, 1; total, 14.

Septic sore throat was reported from: Boston, 6; Brockton, 1; Malden, 1; Natick, 1; Swampscott, 1; total, 10.

Tetanus was reported from: Springfield, 1; total, 1.

Trachoma was reported from: Medford, 1; total, 1.

Tularemia was reported from: Falmouth, 1; total, 1.

Typhoid fever was reported from: Brookfield, 1; Dartmouth, 1; Medford, 1; New Bedford, 1; total, 4.

Typhus fever was reported from: Chelsea, 1; total, 1.

Undulant fever was reported from: Adams, 1; Franklin, 1; Methuen, 1; Southbridge, 1; Southwick, 2; total, 6.

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

Clinic	Date	Clinic Consultant
Haverhill	December 1	William T. Green
Lowell	December 3	Albert H. Brewster
Salem	December 6	Paul W. Hugenberger
Brockton	December 9	George W. Van Gorder
Springfield	December 15	Garry deN. Hough, Jr.
Worcester	December 17	John W. O'Meara
Pittsfield	December 20	Frank A. Slowick
Fall River	December 27	Eugene A. McCarthy
Hyannis	December 28	Paul L. Norton

WAR ACTIVITIES

CIVILIAN DEFENSE

Manual on Emergency Care of Injured

The immediate care that can be given to injured persons at the site of a disaster and the technics of transporting them to safety and medical attention are described in a new manual issued by the Medical Division, Office of Civilian Defense. The work is based on procedures and organization developed by the OCD and on careful study of three years of British and other air-raid experience. The 117-page book is divided into three parts: "Civilian Defense," "Emergency Field Care," and "Transportation of the Injured."

Part I describes the organization and operation of the field casualty service developed by the Medical Division, which includes mobile medical teams, based on hospitals wherever possible; express parties, made up of a medical team, a rescue squad, an ambulance, and a car for sitting cases, dispatched through the control center to a disaster for immediate action; casualty stations for the care of casualties with minor injuries; stretcher teams; and ambulances.

Part II includes a discussion of the injuries and conditions most frequently encountered in wartime disasters — namely, hemorrhage, shock, fractures, burns, suffocation and carbon monoxide poisoning. There are chapters on principles of bandaging, with detailed illustrations; marking of casualties and disposal of the dead; methods of blanketing a casualty; and methods of lashing a casualty to a stretcher.

Special attention is given to crush and blast injuries. Crushing wounds may result from falling masonry, girders, beams or whole floors dislodged by bomb explosions. Although these injuries may be immediately fatal, casualties often show little sign of injury when released, the manual points out. Their condition may appear good for a few hours and yet they may die of kidney failure several days later. Directions for first aid are included, and workers are warned that any person who has been trapped by debris which has pressed on any part of the body must be regarded as a serious casualty. The importance of administering by mouth abundant quantities of fluids and alkalies (sodium bicarbonate) is stressed. Persons exposed to blast from high explosives may also suffer serious internal injury without external evidence of it. The manual urges all persons concerned with the handling of casualties to suspect blast injuries in every person found near the site of a bomb explosion, especially those who have obviously suffered injury and yet show no external evidence of it. More extensive discussions of these two types of injury are included in the recent OCD publication, *Clinical Recognition and Treatment of Shock*.

Part III, devoted to transportation of the injured, describes regular and improvised stretchers and gives directions for stretcher bearing, with a separate section on types of injury that require special care in moving. Another chapter explains methods of carrying the injured without stretchers, and the final chapter explains the ambulance

service of the civilian-defense organization and presents specific instructions for loading and unloading ambulances. The latter instructions describe procedures required if war gases are encountered.

The manual is intended primarily for the training of rescue workers, medical auxiliaries, ambulance drivers and attendants, and stretcher bearers of the Emergency Medical Service. In the appendix are a schedule of training based on the manual; the OCD operations letters describing the work of stretcher teams, the Rescue Service and instructions on self-aid in case of exposure to war gas; and a section on electrical hazards.

MISCELLANY

GRANT TO PROMOTE MEDICAL INFORMATION

Dr. Ross G. Harrison, chairman of the National Research Council, has announced the acceptance by the Council of a grant from the Johnson and Johnson Research Foundation in the amount of $75,000. The grant was made to enable the Division of Medical Sciences, under the chairmanship of Dr. Lewis H. Weed, to gather medical information pertaining to the war effort and to disseminate summaries. The program of the Division of Medical Sciences of the National Research Council contemplates coverage of the various medical reports and bulletins that emanate from civilian and military activities throughout the world. The enterprise should fill a much needed gap in the war effort in medicine, since one of the greatest difficulties encountered in medicine today lies in providing adequate up-to-date information to the medical officers of the armed services, both in this country and abroad, and in making the experience of war medicine available, so far as possible, to civilian physicians.

The Johnson and Johnson Research Foundation appropriation to the National Research Council becomes immediately available; in accordance with present plans it will be utilized in the period up to June 30, 1945. A central office will be established in Washington and reporters will be appointed in various foreign countries, so that a staff of special observers abroad will be working under the direction of the central office. The various theaters of operation present medical problems in which climate, season of year, distribution of insects and distribution of disease, all play different roles. Reports from widely separated parts of the world will be of the greatest medical importance and it is hoped that with the combined effort much of significance will be achieved.

AMA MEETING IN 1944

The Board of Trustees have recently announced that the 1944 annual session of the American Medical Association will be held in Chicago, June 12 to 16. The scheduled meeting place, St. Louis, had to be given up, owing to lack of adequate accommodations. The meetings of the House of Delegates will be held at the Palmer House, which will also house the Scientific Exhibit. The Technical Exposition will be installed at the Stevens Hotel.

The Scientific Exhibit will cover all phases of medicine and the medical sciences with particular emphasis on graduate medical instruction for the physician in general practice. Application blanks for space in the exhibit are now available and may be obtained by communicating with the Director, Scientific Exhibit, American Medical Association, 535 North Dearborn Street, Chicago 10.

BOOK REVIEWS

Air-Borne Infection: Some observations on its decline. By Dwight O'Hara, M.D. 8°, cloth, 114 pp., with 11 charts. New York: The Commonwealth Fund, 1943. $1.50.

The author challengingly but plausibly includes in this series of essays on air-borne infection not only a consideration of the scope of preventive medicine but also chapters on smallpox, streptococcal infections, rheumatic fever and the aging process, in addition to his discussion of upper respiratory infections and tuberculosis. He suggests that preventive medicine has enjoyed over the years the company of a silent partner, and attempts to analyze the spontaneous or indirect factors that have influenced the results of man's conscious effort at control of infection. Health — the physiologic integrity of the tissues — must not be confused with the mere control of conditions prejudicial to health.

This book will wear well because it thoughtfully interprets some rather striking factual data. The contributions of some investigators rust out because their squeaking metallic facts are not sufficiently oiled with interpretive thought. This little volume is well lubricated. It is also well written, and in this respect, as well as in thought and content, it follows in the tradition of such contributions as that of Bigelow on self-limited diseases. It will be read with pleasure and profit by all who are concerned with the problem of keeping men alive and well.

Biochemistry and Morphogenesis. By Joseph Needham, F.R.S. 4°, cloth, 787 pp., with 328 illustrations. Cambridge, England: University Press, 1942. $12.50.

No laboratory should be without this most important work, which deals with one of the fundamental problems of biology by a distinguished investigator. The purpose of the author is to show that the disciplines of chemistry and morphology are closely related. This object is achieved by bringing together the experimental evidence that shows that levels of organization are not alone anatomical but molecular, colloidal, paracrystalline, protein structural and fibrous macromolecular. All these orders are the natural consequence of the properties of matter.

The present study considers the chemical changes that go on during embryonic development. In 1931 the first successful embryonic inductions were obtained; this opened the way to the biochemical investigation of morphogenetic hormones. These substances are discussed in Part 1 under the heading of "The Morphogenetic Substratum." Part 2 deals with "The Morphogenetic Stimuli," that is, the isolation of the inductor substances. Part 3 discusses "The Morphogenetic Mechanisms."

There is a valuable glossary of 8 pages, and an excellent bibliography covers 70 pages. In addition there is a general index, as well as an index of animals, plants and genes. Every student of biology will find this book invaluable.

(Notices on page xii)

Smooth as the drifting clouds

In therapeutic doses, **Alurate** (allyl-isopropylbarbituric acid) does not depress circulation or respiration. Most of the dose is rapidly destroyed, and the remainder is so promptly eliminated that likelihood of "hang-over" or cumulative effect is greatly reduced. For ordinary purposes give one grain at the time sleep is desired—not before. Customary therapeutic doses do not cause sleep beyond the normal period. A good night's sleep is assured with a characteristic feeling of well-being and clear-headedness on awakening.

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NOTICES

BOSTON MEDICAL HISTORY CLUB

There will be a meeting of the Boston Medical History Club at the Boston Medical Library, Sprague Hall, 8 Fenway, on Monday, November 29, at 8 p.m. Mr. James F. Ballard will speak on the subject, "English Medical Books of the Sixteenth Century."

All interested persons are cordially invited to attend.

BOSTON DISPENSARY

A clinical staff meeting of the Boston Dispensary will be held at the Pratt Hospital Auditorium on Friday, November 26, at 12:30 p.m. Dr. Jacob H. Swartz will speak on the subject, "Elements of Medical Mycology." Luncheon will be served at 12 noon.

All interested persons are cordially invited to attend.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 25

FRIDAY, NOVEMBER 26

*9:00–10:00 a.m. Certain Limitations of Medical Case Study. Dr. Ralph E. Wheeler. Joseph H. Pratt Diagnostic Hospital.

*12:30 p.m. Elements of Medical Mycology. Dr. Jacob H. Swartz. Boston Dispensary.

SATURDAY, NOVEMBER 27

*10:00–11:30 a.m. Medical staff rounds. Peter Bent Brigham Hospital.

MONDAY, NOVEMBER 29

*8:00 p.m. English Medical Books of the Sixteenth Century. James F. Ballard Boston Medical History Club. Boston Medical Library, 8 Fenway, Boston.

*8:15 p.m. New England Heart Association. Boston Medical Library, 8 Fenway, Boston.

TUESDAY, NOVEMBER 30

*9:00–10:00 a.m. Medical clinic. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

2:00–4:00 p.m. Myasthenia gravis clinic. Out Patient Department. Massachusetts General Hospital.

WEDNESDAY, DECEMBER 1

*12:00 m. Clinicopathological conference. Children's Hospital.

*Open to the medical profession.

DECEMBER 2. Boston Gastroenterological Society. Page xii, issue of November 4.

DECEMBER 9. Treatment of Allergy. Dr. Francis M. Rackemann. Pennacook Association of Physicians. 8:30 p.m. Haverhill.

FEBRUARY 12. American Board of Obstetrics and Gynecology. Page ix, issue of October 28.

MAY 23 and 24. Massachusetts Medical Society. Annual meeting, Hotel Statler, Boston.

JUNE 12–16. American Medical Association. Annual meeting, Chicago. Page 798.

DISTRICT MEDICAL SOCIETIES

SUFFOLK

DECEMBER 2. Censors' meeting. Page x, issue of September 16

WORCESTER

DECEMBER 8. Worcester City Hospital.
JANUARY 12. Memorial Hospital, Worcester.
FEBRUARY 9. Worcester State Hospital, Worcester.
MARCH 8. St. Vincent Hospital, Worcester.
APRIL 12. Hahnemann Hospital, Worcester.
MAY 10. Annual Meeting.

(Books Received on page xv)

50
MICRO-ACETABS
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BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Hormones in Human Reproduction. By George W. Corner, M.D. 8°, cloth, 265 pp., with 24 plates and 32 illustrations. Princeton, New Jersey: Princeton University Press, 1942. $2.75.

This is the first comprehensive account for the general reader concerning the nature and function of hormones in the processes of sex and reproduction. The book is especially designed for the layman with no previous medical background. The author first describes the reproduction of simple animals and then leads up to the more complicated systems in higher animals, showing how the various organs and functions of the reproductive system are controlled and timed by means of the hormones. Because of its thoroughness the book provides a general account of reproduction in the human race and in the higher animals. The lay reader will find interesting discussion of such particular subjects as the nature of sex, heredity and the development of the human embryo. The work should prove of value to the biologist, physician and biochemist, as well as the layman. The use of larger type in printing would have made the volume easier to use by the general reader, who is unaccustomed to scientific writing.

A Manual of Cardiology. By Thomas J. Dry, M.B., Ch.B., M.S. (in medicine), assistant professor of medicine, University of Minnesota (Mayo Foundation), and consultant in Section on Cardiology, Mayo Clinic. 8°, cloth, 310 pp., with 80 illustrations. Philadelphia and London: W. B. Saunders Company, 1943. $3.00.

This manual is intended for those who feel that the problems of heart disease are too complex and extensive to be grouped easily, and who do not wish to use the large treatises on the subject. The various disorders that produce similar disturbances of function and similar objective phenomena are grouped together, and features that distinguish these conditions from one another are, whenever possible, illustrated graphically. The emphasis is placed on diagnosis and prognosis.

Urology in General Practice. By Nelse F. Ockerblad, M.D., professor of clinical urology, University of Kansas School of Medicine, senior attending urologist, St. Luke's Hospital, and consulting urologist, Children's Mercy Hospital, Kansas City, Missouri; and Hjalmar E. Carlson, M.D., instructor in urology, University of Kansas School of Medicine, and attending urologist, St. Luke's Hospital and Trinity Lutheran Hospital, Kansas City, Missouri. 8°, cloth, 383 pp., with 98 illustrations. Chicago: The Year Book Publishers, Incorporated, 1943. $4.00.

This is one of a series of general-practice manuals written in a dogmatic manner. It is not documented and is free of quotations from the literature, historical material and statistics. It is frankly a personal book based on a combined experience of forty years of practice and is intended for the general practitioner and medical student.

(Continued on page xix)

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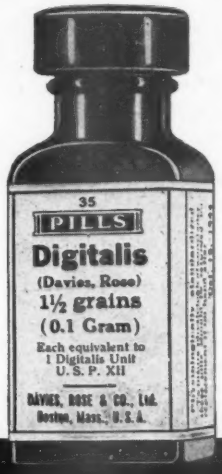

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Manual of Veterinary Bacteriology. By Raymond A. Kelser, D.V.M., A.M., Ph.D., brigadier general, Army of the United States, and chief, Veterinary Division, Surgeon General's Office, War Department, Washington, D. C.; and Harry W. Schoening, V.M.D., chief, Pathological Division, Bureau of Animal Industry, and assistant chief, Bureau of Animal Industry, United States Department of Agriculture, Washington, D. C. Fourth edition. 8°, cloth, 719 pp., with 94 illustrations and 11 tables. Baltimore: The Williams and Wilkins Company, 1943. $6.50.

This fourth edition of an authoritative work has been thoroughly revised and brought up to date by the inclusion of much new material.

Group Differences in Urban Fertility: A study derived from the National Health Survey. By Clyde V. Kiser, member, Technical Staff, Milbank Memorial Fund. 8°, cloth, 284 pp. Baltimore: The Williams and Wilkins Company, 1942. $2.50.

This monograph is based on the large mass of fertility data collected by the National Health Survey in 1935–1936. The survey covered some 700,000 families in eighty-three cities in eighteen states. It was undertaken primarily as a study of the incidence and severity of illness in different elements of the urban population, but secured records of births during the year preceding enumeration, as well as a variety of other data. Various limitations of the fertility data collected by the survey are described in this report. The urban population is collectively characterized by a low level of reproduction; so low that without replenishment from rural areas it would ultimately fail by a wide margin to reproduce itself. In general, there is fair evidence that group differences in fertility are tending to diminish rather than to increase and that this is probably due to the widening spread of contraceptive practice. This highly technical study of marital fertility rates is, in all aspects, an important contribution to the subject and is recommended as an authoritative source book.

The Therapy of the Neuroses and Psychoses: A socio-psycho-biologic analysis and resynthesis. By Samuel H. Kraines, M.D., associate in psychiatry, University of Illinois College of Medicine, assistant state alienist, State of Illinois, and captain, Medical Corps, Army of the United States. Second edition. 8°, cloth, 567 pp. Philadelphia: Lea and Febiger, 1943. $5.50.

This second edition has been expanded by the inclusion of new material on schizophrenia and by the addition of new chapters on the shock therapies; the organic psychoses and the neuropsychiatric states induced by the war. The chapter on psychoanalysis and related schools has been deleted to provide space for the new material.

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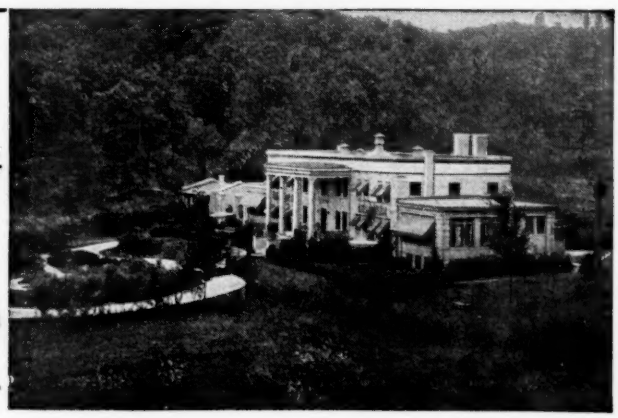

1+1=1

To state it another way:

ONE	ONE	ONE
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